STATISTICAL ANALYSIS PLAN

SCYNEXIS, Inc.
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Open-Label Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics of SCY078 in Patients with Candidiasis, Including Candidemia, Caused by *Candida auris*

SCYNEXIS Clinical Protocol No. SCY-078-305

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Prepared by

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STATISTICAL ANALYSIS PLAN DOCUMENT HISTORY

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SIGNATURE PAGE

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate transaminase
BID	twice a day
BMI	body mass index
CI	confidence interval
CRF	case report form
CSR	clinical study report
DRC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report forms
e-diary	electronic diary
EoT	end of treatment
ET	early termination
HR	heart rate
ITT	intent-to-treat
IV	intravenous
LOCF	last observation carried forward
max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
min	minimum
n	number of subjects
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
WHOCC	World Health Organization Collaborating Centre

1. Introduction

Candida is among the most common causes of healthcare-associated bloodstream infections in the United States (US), with an estimate of 46,000 healthcare-associated *Candida* infections occurring among hospitalized patients in the US each year. The CDC surveillance data have reported that approximately 7% of all *Candida* bloodstream isolates tested are resistant to fluconazole and some *Candida* strains are increasingly resistant to first-line and second-line antifungal treatment agents, including azoles and echinocandins.[1] Centers specialized in the treatment of immune-compromised patients report increased frequency of non-*albicans* species of *Candida* with higher incidence of resistance. For example, in a survey conducted in the MD Anderson Cancer Center, Houston, Texas, US (2005–2013), out of 146 isolates of *C. glabrata* evaluated, 30 (20.5%) were resistant to fluconazole; 15 (10.3%), to caspofungin; and 10 (6.8%), to multiple drugs.[2] Roughly, 30% of patients with drug-resistant *Candida* bloodstream infections (candidemia) due to drug-resistant *Candida* die during their hospitalization.

Candida auris is an emerging fungus that presents a serious global health threat. Healthcare facilities in several countries have reported that *C. auris* has caused severe illness in hospitalized patients. Some strains of *Candida auris* are resistant to all three major classes of antifungal drugs. This type of multidrug resistance has not been seen before in other species of *Candida*. Also of concern, C. *auris* can persist on surfaces in healthcare environments and spread between patients in healthcare facilities, unlike most other *Candida* species.[3]

SCY-078 (now known as ibrexafungerp) is a member of a new class of antifungal agents and is an orally active, semi-synthetic, triterpene derivative of the natural product enfumafungin. Ibrexafungerp is a structurally distinct class of glucan synthase inhibitor 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.

While three classes of antifungal agents (azoles, echinocandins and polyenes) are currently available to treat *Candida* infections, only azoles are available for oral therapy 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 as well as the toxicity associated with polyenes, signals the need for new agents that are well tolerated and retain activity against resistant strains. Ibrexafungerp represents the first compound of the triterpene class of β-(1,3)-D-glucan synthesis inhibitors in development for the treatment of fungal infections. It is structurally distinct and retains activity *in vitro* against both azole-resistant and, importantly, 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* and *Aspergillus* species and, as such, it would represent the first oral non-azole treatment alternative for these infections. Ibrexafungerp is being developed as the first oral and intravenous

(IV) glucan synthase inhibitor for the treatment and prevention of fungal infections caused by *Candida* and *Aspergillus* species with the potential to provide the therapeutic advantages of both an IV and oral formulation.

This study is being conducted to evaluate the efficacy, safety, tolerability and PK (for a subset of subjects) of ibrexafungerp in male and female subjects >18 years of age with a documented *Candida auris* infection. Due to the COVID pandemic causing major delays with shipping of samples to the testing laboratory, PK samples could not be analysed within the required testing window, and PK analysis is therefore not described in the statistical analysis plan (SAP).

The purpose of this 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. Changes made to the SAP after it has been signed but prior to database lock will be documented in a SAP amendment. Changes made to the analyses after database lock will be described in the CSR. Additional exploratory analyses which aren't listed in the protocol are planned as outlined in Section 7.3.1. Table shells and data set specifications will be prepared on the basis of this document.

2. Study Objectives

2.1 Primary Objectives

The primary objective is to evaluate the efficacy of ibrexafungerp as determined by a Data Review Committee (DRC) by assessing global success (composite assessment of clinical and mycological success) at End of Treatment (EoT).

2.2 Secondary Objectives

2.2.1 Secondary Objectives

- To evaluate the safety and tolerability of ibrexafungerp
- To evaluate the efficacy of ibrexafungerp by measuring recurrence of the baseline fungal infection 42 days after EoT (Week 6 Follow up)
- To determine the efficacy of ibrexafungerp by measuring subject survival 42 and 84 days after Day 1 (first dose of study drug)

2.2.2 Exploratory Objectives

- To evaluate the efficacy of ibrexafungerp as determined by the DRC by assessing additional efficacy outcomes at EoT

- To evaluate the efficacy of ibrexafungerp as determined by the investigator by assessing select efficacy outcomes at EoT
- To determine the interpretative breakpoint of ibrexafungerp against *C. auris*

2.3 Study Design

This is a multicenter, open-label, non-comparator, single-arm study to evaluate the efficacy, safety, tolerability and PK (for a subset of subjects) of ibrexafungerp in male and female subjects ≥18 years of age with a documented *Candida auris* infection.

Subjects must have a documented candidiasis, including candidemia, caused by *Candida auris* to be considered for enrollment. Subjects are also eligible if they are receiving IV antifungal therapy for their *C. auris* infection and, in the judgment of the investigator, continued IV antifungal therapy is not feasible or desirable due to clinical or logistical circumstances. Additionally, subjects must be able to tolerate medication orally or through a nasogastric (NG) tube or percutaneous endoscopic gastrostomy (PEG) tube to be able to participate in the study.

Subjects must meet all study criteria to be eligible for inclusion. Inclusion of each subject in the study must be approved by the Sponsor prior to enrollment.

The study will be conducted at approximately 10 sites globally, and is planned to enroll and treat approximately 30 subjects.

Study Schedule

The study will consist of a combined Screening and Treatment Day 1 (Baseline) visit to determine subject eligibility and begin study treatment; a Treatment Day 2 visit for PK sampling (only for subjects who participate in the PK portion of the study); 2 additional scheduled treatment visits (Treatment Days 3 to 5 and Treatment Days 7 to 10) and treatment visits every 14 days thereafter (for up to a total of 90 days) to continue study treatment and perform clinical, mycological, imaging, serological and safety assessments, and to collect PK samples (only for subjects who participate in the PK portion of the study); an EoT visit to assess primary and exploratory efficacy outcomes; 1 follow-up (FU) visit 6 weeks after EoT (Week 6 Follow-up) to assess recurrence (secondary efficacy endpoint) and safety; and 2 survival visits/contacts to determine survival status (alive or deceased).

Study Treatments

This is an open-label, single-arm study. All enrolled subjects will receive an initial oral loading dose of 750 mg of ibrexafungerp (3 tablets of 250 mg) BID during the first 2 days of treatment

and then subsequent oral doses of 750 mg QD for up to 90 days.

For subjects who are unable to take oral medications, tablets may be crushed and administered with approximately 8 oz./240 mL of water via an NG or PEG tube. The tube should be closed at least one hour before drug administration and be flushed with approximately 8 oz./240 mL of water before and after drug administration.

Oral treatment may be given on an inpatient or outpatient basis, as needed, and for as long as is clinically indicated, at the investigator´s discretion, but in no event for more than a total of 90 days of antifungal treatment.

2.4 Study Timepoints

Detailed schedules of all study visits and procedures are presented in the Schedules of Treatment Visits and Procedures (Table 1 and Table 2)

Table 1 Schedule of Treatment Visits and Procedures (Study SCY-078-305)

PROCEDURE Visit	Visit 1 **Screening/ Treatment Day 1 (Baseline)**	Visit 2 **Treatment Day 2** (PK Subset only)	Visit 3 **Treatment Days 3 to 5**	Visit 4 **Treatment Days 7 to 10**	Visit 5-10 **Every 14 days** during Treatment	**EoT** Day	**Week 6 Follow-up** (6 weeks after EoT)	**Unscheduled** Visits/
Days (allowable window)	Day -1 to Day 1				± 2 days	± 2 days	± 2 days	
Informed Consent	X[a]							
Inclusion/Exclusion Criteria	X[a]							
Subject Enrollment and ID Assignment	X[a]							
Medical History and Demographics	X[a]							
General Physical exam	X[a]					X	X	
Vital Signs	X[a]					X		If applic.
12-Lead ECG	X[a]					X		If applic.
Pregnancy Test	X[a]					X		
Targeted Physical Exam including Clinical Evaluation of Signs and Symptoms of Infection	X[a]		X	X	X	X	X	
All Mycological Testing	X[a]		If applic.	If applic.	If applic.	If applic.	If applic.	If applic.
Imaging (if applicable)	X[a]		If applic.	If applic.	If applic.	X	If applic.	If applic.
Serological Testing	X[a]		If applic.	If applic.	If applic.	X	If applic.	If applic.
Clinical Safety Laboratory Assessments (hematology, blood chemistry, urinalysis)	X[a]			X	If applic.	X	If applic.	If applic.
Pharmacokinetic Assessments (PK Subset only)[b]		X	X	X				
Efficacy Assessment						X	X	
Study Drug Dispensing	X		X	X	X			
Study Drug Dosing[c]	X----------					----------X		
Study Drug Collection and Treatment Compliance Evaluation		X	X	X	X	X		X
Subject Diary Dispensing, Collection and Review	X			X	X	X		X
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X

PROCEDURE Visit	Visit 1 **Screening/ Treatment Day 1 (Baseline)**	Visit 2 **Treatment Day 2** (PK Subset only)	Visit 3 **Treatment Days 3 to 5**	Visit 4 **Treatment Days 7 to 10**	Visit 5-10 **Every 14 days** during Treatment	**EoT** Day	**Week 6 Follow-up** (6 weeks after EoT)	**Unscheduled** Visits/
Days (allowable window)	Day -1 to Day 1				± 2 days	± 2 days	± 2 days	
Adverse Event Monitoring	X	X	X	X	X	X	X	X

Abbreviations: AE=adverse event; applic.= applicable; ECG=electrocardiogram; EoT=end of treatment; PK = pharmacokinetic(s).

a. Conducted prior to first study drug dosing
b. PK testing will be conducted for subjects who give their consent to participate in the PK portion of the study (the PK Subset). Sparse PK samples for Population PK analysis will be collected at the following visits and sampling windows: on Treatment Day 2 (one sample collected anytime post dosing); between Treatment Days 3 to 5 (one sample collected predose on any of these days) and between Treatment Days 7 to 10 (one sample collected predose). The time of dosing and sample collection must be recorded on the subject diary and eCRF.
c. All enrolled subjects will receive an initial oral loading dose of 750 mg of SCY-078 (3 tablets of 250 mg) BID during the first 2 days of treatment and then subsequent oral doses of 750 mg QD for up to 90 days.

Table 1 Schedule of Survival Visits and Procedures (Study SCY-078-305)

PROCEDURE Visit	Visit/contact **Survival Day 42**	Visit/contact **Survival Day 84**
Days (allowable window)	± 2	± 2
Subject Status (alive/ deceased)	X	X

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.

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 calculation was performed.

Approximately 10 study centers worldwide are expected to participate in subject enrollment and treatment. The study is planned to enroll and treat approximately 30 subjects.

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.

Per-Protocol Population: The per-protocol (PP) population will include all ITT subjects who receive at least 10 total days of antifungal therapy (ibrexafungerp), who have an EoT assessment and who have no major protocol violations that would impact the assessment of efficacy.

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 (PK) Population: There will be no PK population since no PK analysis were conducted during the study.

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

Subject disposition in terms of the number and percentage of subjects enrolled by site will be tabulated. The number of subjects enrolled, number completing the study and reasons for discontinuation will be summarized.

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, weight, height, BMI, and country 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) 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.

5.4 Fungal Disease

The fungal disease and site of infection, as confirmed by the DRC, will be presented in a listing.

5.5 Enrollment Categories

The enrollment categories, as confirmed by the DRC, will be presented in a listing.

5.6 Evidence of Ongoing Infection at Baseline

The evidence of ongoing infection at Baseline, as confirmed by the DRC, will be summarized in a table and 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 28 days before Baseline/Day 1 through EoT will be recorded on the eCRF. 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. 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 web-based version of the World Health Organization Collaborating Centre (WHOCC) ATC/DDD Index 2023 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 – first dose 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 last dose date – first dose date + 1.

The cumulative doses taken across the treatment period will use the exposure and missed dose log. All enrolled subjects will receive an initial oral loading dose of 750 mg of ibrexafungerp (3 tablets of 250 mg) BID during the first 2 days of treatment and then subsequent oral doses of 750 mg QD for up to 90 days. 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 is defined as 2 doses for the first 2 days and then 1 dose for up to 90 days.

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 and PP populations. The ITT analyses will be considered primary and the 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 Success at EOT, as determined by the DRC. Secondary efficacy endpoints include the percentage of subjects with a recurrence of the baseline fungal infection 42 days after EoT (Week 6 Follow up) as determined by the DRC, and the percentage of subjects surviving 42 and 84 days after Day 1 (first dose of study drug).

Efficacy outcomes will be based on definitions captured in Table 3. Criteria for the Investigator is outlined in Section 7.3.

Additional efficacy endpoints to be evaluated are in Section 7.3.

7.1 Primary Endpoint

The primary efficacy objective is to evaluate the efficacy of ibrexafungerp as determined by a DRC by assessing global success (composite assessment of clinical and mycological success) at EoT. The primary efficacy endpoint of the study is the percentage of subjects with global success (complete or partial global response) at EoT as determined by the DRC. Global outcome will be scored as global success (complete global response or partial global response) or global failure (stable disease or progressive disease) or Unable to determine – due to missing data.

Table 3 Global Outcome

Global Response	**Outcome Criteria**
Success	Complete Global Response: Complete clinical response (the resolution of all clinical signs and symptoms and/or radiological abnormalities from baseline attributable to the *Candida auris* infection) and a mycological response (mycological clearance (direct and/or negative cultures [when obtainable] and/or normal serological results [when appropriate])
	Partial Global Response: Partial clinical response (major improvement of all clinical signs and symptoms and/or radiological abnormalities from baseline attributable to the *Candida auris* infection) and a mycological response (mycological clearance (direct and/or negative cultures [when obtainable] and/or normal serological results [when appropriate])
Failure	Stable Disease: Minor or no clinical improvement but without deterioration and/or unchanged serological response.
	Progressive Disease: 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.
[a]Not Evaluable	Outcome cannot be assessed due to missing data

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

7.1.1 Primary Analysis

The primary efficacy analysis will be performed at EoT. A responder analysis will be performed on the number and percentage of subjects with Successful Global Response as determined by the DRC will be presented 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.

If Global Response has not been deemed a success or failure, the outcome will be categorized as not evaluable. A responder is defined as a subject with either a success or a failure. A response of not evaluable will not be included in the analysis.

7.2 Secondary Endpoints

Secondary efficacy assessment includes recurrence (after EoT) and survival.

The percentage of subjects with a recurrence of the baseline fungal infection 42 days after EoT (Week 6 Follow up) as determined by the DRC will be presented with 95% CIs for the ITT and PP populations using the same approach as for the primary endpoint. Recurrence is defined as global success at EoT but re-emergence of the baseline *Candida auris* infection during the post treatment follow-up. Re-emergence of the *Candida auris* infection is required to be with the same species and involving the same site that was initially identified at Screening/Treatment Day 1.

The percentage of subjects surviving at the defined time points will be presented for the 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. The probability of survival will be calculated at 42 and 84 days after Day 1 (first dose of study drug).

7.3 Exploratory Endpoints

Exploratory categorical endpoints will be presented with 95% CIs for the ITT and PP populations using the same approach as for the primary endpoint.

7.3.1 Exploratory Analyses

A responder analysis will be performed on the following endpoints. If the outcome cannot be assessed due to missing data, it will be categorized as not evaluable. A responder is defined as a subject with a response other than not evaluable. A response of not evaluable will not be included in the analysis.

- Percentage of subjects for each global response (complete response, partial response, stable disease, progressive disease) EoT, as determined by the DRC
- Percentage of subjects with clinical success at EoT, as determined by the investigator and DRC
- Percentage of subjects for each clinical response (complete response, partial response, stable response, progression of fungal disease, death) at EoT, as determined by the DRC

- Percentage of subjects with mycological success at EoT, as determined by the investigator and DRC
- Percentage of subjects with global success at EoT, as determined by the investigator

Additional exploratory analyses:

- All cause mortality at Day 30
- Analysis of response by minimum inhibitory concentration (MIC) based on CLSI M27-A3 *in vitro* method and EUCAST method at Screening

The following exploratory analyses were not originally included in the protocol:

- Evidence of ongoing infection at Baseline as determined by the DRC
- Causal relationship of death in the opinion of the DRC (if death is reported at any time during the study)
- Global response by site of infection (candidemia only, Pleural/Pulmonary, Intra-abdominal/Pelvic, Soft tissue/wound, Bone and joint, Urinary tract, other)
- Global response by reason for enrollment (primary, refractory, intolerance to SOC, stepdown)
- Global response by region (India, Pakistan, South Africa)
- Global response by Age (,65; >= 65 years)
- Global response by neutropenia (ANC < 500) vs non neutropenic

7.3.2 Clinical and Mycological Outcome

Clinical success is defined as a complete clinical response (the resolution of all clinical signs and symptoms and/or radiological abnormalities from baseline attributable to the *Candida auris* infection) or a partial clinical response (major improvement of all clinical signs and symptoms and/or radiological abnormalities from baseline attributable to the *Candida* auris infection).

Mycological success is defined as a mycological response (mycological clearance (direct and/or negative cultures [when obtainable] and/or normal serological results [when appropriate]).

8. Safety

The safety analyses will be performed on all subjects in the safety population. Analyses will be based on physical exam, vital signs, 12-lead ECGs, safety laboratory tests (hematology, blood chemistry and urinalysis), concomitant medications, AEs and treatment discontinuations. 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). 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 be 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. Samples for clinical laboratory tests will be collected at Screening, Days 7 to 10, 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.

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

Female subjects of child-bearing potential will have urine pregnancy tests conducted at screening and at any timepoints during the study, if needed. Only subjects with negative pregnancy test results will be enrolled. Any subjects with positive pregnancy test results at any time during the study will be presented in a listing.

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), and pulse rate (bpm) 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

A general physical examination will be conducted at Screening, EoT, and at the 6-Week FU visits. The physical examination will include an abbreviated assessment of general appearance, skin, eyes, heart, chest, and abdomen.

All abbreviated physical examinations will be classified as Normal, and Abnormal. Any abnormalities noted during the physical examination will be presented in a listing for all subjects.

8.5 12-lead Electrocardiogram

Summary tables will be presented for QTcF for subjects in the safety population. Observed results at the scheduled visits and changes from baseline to post-baseline visits will be presented. All ECG data by subject will be presented in a listing.

9. Interim Analysis and Supplemental Analysis

No interim analysis is planned for this study.

10. Tables, Listings, and Figures

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