SCYNEXIS, Inc.

Clinical Trial Protocol

Open-Label Study to Evaluate the Efficacy, Safety, Tolerability and Pharmacokinetics of SCY 078 in Patients with Candidiasis, Including Candidemia, Caused by *Candida auris*

SCYNEXIS Protocol Number SCY-078-305

SCYNEXIS, Inc.

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1.0 Contact Information

Contract Research Organization	
Study Medical Monitor	
Clinical Project Manager	
Safety Contact **Sponsor**	

2.0 Protocol Approvals

PROTOCOL ID: SCY-078-305

Open-Label Study to Evaluate the Efficacy, Safety, Tolerability and Pharmacokinetics of SCY 078 in Patients with Candidiasis, Including Candidemia, Caused by *Candida auris*

SCYNEXIS, Inc. Approval:

_____ _____
Date

Investigator Agreement Statement

PROTOCOL ID: SCY-078-305

Open-Label Study to Evaluate the Efficacy, Safety, Tolerability and Pharmacokinetics of SCY 078 in Patients with Candidiasis, Including Candidemia, Caused by *Candida auris*

I understand that all documentation provided to me by SCYNEXIS, Inc. or its designated representative(s) concerning this study that has not been published previously will be kept in the strictest confidence. This documentation includes the study protocol, Investigator's Brochure, case report forms, and other scientific data. This study will not commence without the prior written approval of a properly constituted Institutional Review Board or Ethics Committee. No changes will be made to the study protocol without the prior written approval of SCYNEXIS, Inc. and the Institutional Review Board/Ethics Committee, except where necessary to eliminate an immediate hazard to the patient. All patients will provide a written informed consent prior to participation.

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

Principal Investigator's Signature	Date

Principal Investigator's Name (Printed)

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4.0 Revision History

Not applicable

6.0 Abbreviations

ABBREVIATION	DEFINITION
aPTT	activated partial thromboplastin
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BID	twice daily
BUN	blood urea nitrogen
CD	compact disk
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CL/F	clearance/fraction
CLSI	Clinical and Laboratory Standards Institute
C_{max}	maximum concentration
CPK	creatine phosphokinase
CRO	contract research organization
CT	computerized tomography
CYP	cytochrome P450
DMC	Data Monitoring Committee
DVD	digital versatile disk
EC	Ethics Committee
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic case report form
EDC	electronic data capture
EoT	end of treatment

ABBREVIATION	DEFINITION
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FDA	Food and Drug Administration
FU	follow-up
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
IB	Investigator´s Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ID	identification
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent to treat
IV	intravenous
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
MRI	magnetic resonance imaging
NG	nasogastric
OTC	over-the-counter
PEG	percutaneous endoscopic gastrostomy
PI	principal investigator
PK	pharmacokinetics
Pop PK	population pharmacokinetics
PP	per protocol
PT	prothrombin time
QD	once daily
QTcF	QTc interval corrected for heart rate using Fridericia´s correction

ABBREVIATION	DEFINITION
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOC	standard of care
TT	thrombin time
ULN	upper limit of normal
US	United States
VVC	vulvovaginal candidiasis
WBC	white blood cell
WT	wild type
β-hCG	β-human chorionic gonadotropin

7.0 Protocol Synopsis

Title: Open-Label Study to Evaluate the Efficacy, Safety, Tolerability and Pharmacokinetics of SCY 078 in Patients with Candidiasis, Including Candidemia, Caused by *Candida auris*

Primary Objectives:

- To evaluate the efficacy of SCY-078 as determined by a Data Monitoring Committee (DMC) by assessing global success (composite assessment of clinical and mycological success) at End of Treatment (EoT).

Secondary Objectives:

- To evaluate the safety and tolerability of SCY-078
- To evaluate the efficacy of SCY-078 by measuring recurrence of the baseline fungal infection 42 days after EoT (Week 6 Follow-up)
- To determine the efficacy of SCY-078 by measuring subject survival 42 and 84 days after Day 1 (first dose of study drug)

Exploratory Objectives

- To evaluate the efficacy of SCY-078 as determined by the DMC by assessing additional efficacy outcomes at EoT
- To evaluate the efficacy of SCY-078 as determined by the investigator by assessing select efficacy outcomes at EoT
- To determine the interpretative breakpoint of SCY-078 against *C. auris*
- To evaluate the pharmacokinetics (PK) of SCY-078 by population PK analysis (for a subset of subjects)

Primary Endpoints:

- Efficacy as measured by the percentage of subjects with global success (complete or partial global response) at EoT as determined by the DMC

Secondary Endpoints:

Safety and tolerability as measured by:

- Physical examination, vital signs, 12-lead electrocardiogram (ECG), safety laboratory tests, adverse events (AEs) and treatment discontinuations
- The percentage of subjects with treatment-emergent AEs

Efficacy as measured by:

- The percentage of subjects with a recurrence of the baseline fungal infection 42 days after EoT (Week 6 Follow up)
- The percentage of subjects surviving 42 and 84 days after Day 1 (first dose of study drug)

Exploratory Endpoints:

- Percentage of subjects with complete global response at EoT, as determined by the DMC
- Percentage of subjects with partial global response at EoT, as determined by the DMC
- Percentage of subjects with stable disease at EoT, as determined by the DMC
- Percentage of subjects with progressive disease at EoT, as determined by the DMC
- Percentage of subjects with clinical success at EoT, as determined by the investigator

- Percentage of subjects with mycological success at EoT, as determined by the investigator
- Percentage of subjects with global success at EoT, as determined by the investigator
- Analysis of response by minimum inhibitory concentration (MIC) based on CLSI M27-A3 *in vitro* method
- SCY-078 plasma concentration by population PK analysis (for a subset of subjects)

Study Phase: 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 SCY-078 in male and female subjects ≥18 years of age with a documented *Candida auris* infection.

Study Population: 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 intravenous (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 Treatments: Eligible subjects will receive an initial oral loading dose of 750 mg of SCY-078 (3 tablets of 250 mg) twice a day (BID) during the first 2 days of treatment and then subsequent oral doses of 750 mg once a day (QD) for up to 90 days.

Study Visits: 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).

Efficacy: Efficacy will be assessed primarily in terms of global success (defined as a complete or partial global [clinical and mycological] response) at EoT as determined by the DMC. Secondary efficacy assessments will include recurrence (after EoT) and survival. Recurrence will be assessed by measuring recurrence of the baseline fungal infection 42 days after EoT (Week 6 FU). Survival will be determined on Day 42 and Day 84 (42 and 84 days after the Screening/Treatment Day 1 visit [first dose of study drug]). This can be an in-person visit or a phone contact, and will document subject status only (alive or deceased). If subject is deceased, the relationship to the fungal infection will be recorded.

Complete global response, partial global response, stable disease and progressive disease at EoT as determined by the DMC will be assessed as exploratory efficacy endpoints. Global success, clinical success and mycological success at EoT as determined by the investigator will also be assessed as exploratory efficacy endpoints.

The following study procedures will be performed to assess treatment outcome: clinical signs and symptoms of candidiasis; radiological assessments including esophagoscopy and other imaging scans, as applicable (e.g., X-ray, ultrasound, CT and MRI); mycological testing (fungal cultures); and serological testing (ß-(1,3)-D glucan).

Pharmacokinetics: PK analyses will be performed for subjects who give their consent to participate in the PK portion of the study (the PK Subset). Blood samples will be collected on Treatment Day 2 (one sample collected anytime post dosing), Treatment Days 3 to 5 (one sample collected predose on any of these days) and Treatment Days 7 to 10 (one sample collected predose on any of these days).

Safety: Subjects will be evaluated for safety throughout the study, including parameters such as physical exam, vital signs, 12-lead ECGs, safety laboratory tests (hematology, blood chemistry and urinalysis), AEs, treatment discontinuations and concomitant medications. A final safety assessment will be conducted at the Week 6 Follow-up visit (6 weeks after the EoT).

Analyses: Results from the study will be analyzed against historical SoC-treated subjects, who will be selected from literature reviews and other data resources, and be based on the 2015 Infectious Diseases Society of America guidelines for the management of candidiasis.

Target Population: Subjects ≥18 years of age with documented candidiasis, including candidemia, caused by *Candida auris*.

KEY Inclusion Criteria:

Subject must fulfill the following **KEY** criteria to be eligible for study admission:

1. Subject is a male or female adult ≥ 18 years of age on the day the study informed consent form (ICF) is signed.
2. Subject has a documented candidiasis, including candidemia, caused by *Candida auris*. The subject is also eligible if he/she is receiving IV antifungal therapy for their *C. auris* infection and, in the judgment of the investigator, long-term IV antifungal therapy is not feasible or desirable due to clinical or logistical circumstances.
   A documented candidiasis, including candidemia, caused by *Candida auris* is defined as the recovery of *Candida auris* by culture of a sample obtained within the last 7 days.
3. Subject is able to tolerate medication orally or through a nasogastric (NG) tube or percutaneous endoscopic gastrostomy (PEG) tube.

KEY Exclusion Criteria:

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

1. Subject has a fungal disease with central nervous system involvement.
2. Subject has a fungal disease of the bone and/or joint that is expected to require >90 days of study drug treatment.
3. Subject has an inappropriately controlled fungal infection source (e.g. persistent catheters, devices, identified abscess) that is likely the source of the fungal infection.
4. Subject is hemodynamically unstable and/or requiring vasopressor medication for blood pressure support.
5. Subject has abnormal liver test parameters: AST or ALT >10 x ULN, and/or total bilirubin >5 x ULN.
   Note: Subjects with unconjugated hyperbilirubinemia with diagnosis of Gilbert's disease **are not excluded**.
6. Subject has an Apache score >16.
7. Subject has serum creatinine >3 times from Baseline (Screening/Treatment Day 1) value.

8. Subject has a prolonged QTcF interval (Fridericia's correction: $QTc = QT/(RR)^{0.33}$) >480 ms on the baseline ECG or other abnormalities deemed clinically significant by the investigator that would put the subject at unacceptable risk for participation in the study.

Study Drugs: SCY-078 citrate drug product for oral administration will be supplied as a tablet containing 250 mg of SCY-078 active ingredient on a free-base basis. In addition to the active ingredient, the tablet formulation also contains silicified microcrystalline cellulose, crospovidone, mannitol, colloidal silicon dioxide, magnesium stearate (non-bovine) and butylated hydroxyanisole.

SCY-078 tablets are to be stored at room temperature, between 15°C and 30°C.

Randomized Treatment Groups: This is an open-label, single-arm study. There will be no randomization or stratification for this study. Eligible subjects must be approved by the sponsor for enrollment.

Subjects will receive an initial oral loading dose of 750 mg of SCY-078 (3 tablets of 250 mg) twice a day (BID) during the first 2 days of treatment and then subsequent oral doses of 750 mg once a day (QD) for up to 90 days.

Study Blinding: Open-label study

Pharmacokinetic Evaluations (PK Subset Only): PK testing will be conducted for subjects who give their consent to participate in the PK portion of the study (the PK Subset). Up to three (3) blood samples will be collected at the following visits and sampling windows: Treatment Day 2 (one sample collected anytime post dosing), Treatment Days 3 to 5 (one sample collected predose on any of these days) and Treatment Days 7 to 10 (one sample collected predose on any of these days).

The sparse samples collected in this study will be analyzed using Population PK (Pop PK) analysis methods to estimate PK parameters (C_{max}, AUC, clearance/fraction absorbed [CL/F]) as applicable.

Efficacy Evaluations: Efficacy will be assessed primarily in terms of global success (defined as a complete or partial global [clinical and mycological] response) at EoT as determined by the DMC. Complete global response, partial global response, stable disease and progressive disease at EoT as determined by the DMC will be assessed as exploratory endpoints. Global success, clinical success and mycological success at EoT as determined by the investigator will also be assessed as exploratory endpoints.

The following treatment outcome definitions will be used for the assessment of efficacy:

Global Outcome

Global outcome will be scored as global success (complete global response or partial global response) or global failure (stable disease or progressive disease)

Global success: Global success is defined as a complete global response or a partial global response

- Complete global response is defined as a complete clinical response (the resolution of all clinical signs and symptoms and/or radiological abnormalities from baseline attributable to 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 is defined as a 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])

Global failure: Global failure is defined as either stable disease and/or progressive disease

- Stable disease is defined as minor or no clinical improvement but without deterioration and/or unchanged serological response.
- Progressive disease is defined as clinical deterioration necessitating alternative antifungal therapy or resulting in death, and/or worsened serological response, and/or persistence of fungal infection on the basis of culture, microscopic evaluation, or histopathological testing.

Clinical Outcome

Clinical success: 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 Outcome

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

Efficacy assessments will also include recurrence (after EoT) and survival. Recurrence will be assessed by measuring recurrence of the baseline fungal infection 42 days after EoT (Week 6 FU). Survival will be determined on Day 42 and Day 84 (42 and 84 days after Screening/Treatment Day 1 [first dose of study drug]).

Recurrence: 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.

Safety Evaluations:

Subjects will be evaluated for safety and tolerability throughout the study, including parameters such as physical exam, vital signs, 12-lead ECGs, safety laboratory tests (hematology, blood chemistry and urinalysis), concomitant medications, AEs and treatment discontinuations.

Statistical Analyses:

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

All analyses of the study results for SCY-078 will be descriptive. Unless otherwise stated, data will be analyzed as is with no imputation.

Sample Size Determination: This is an exploratory study and no formal sample size calculation was performed. A total of 30 subjects are estimated to be adequate for an assessment of the safety and tolerability of SCY-078 in subjects with candidiasis, including candidemia, caused by *C. auris*.

Analysis Populations:

- **Intent-to-Treat (ITT) Population**: The ITT population will include all subjects who are enrolled in the study.
- **Per-Protocol (PP) Population**: The PP population will include all ITT subjects who receive at least 10 total days of antifungal therapy (SCY-078), 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.

- **PK Population**: The PK population will include all enrolled subjects who provide at least one PK sample.

Pharmacokinetic Analyses (PK Subset Only):
The PK analysis will be conducted on the PK Population. The concentration versus time data from the sparse PK samples collected in this study will be analyzed using a Pop PK model to estimate C_{max}, AUC and CL/F, as applicable. Further analysis of possible metabolites may be performed.

Efficacy Analyses:
The primary efficacy endpoint, the percentage of subjects with global success (defined as a complete or partial global [clinical and mycological] response) as determined by the DMC at EoT, will be presented with a 95% confidence interval (CI) for the ITT and PP populations.
Secondary and exploratory categorical endpoints will be presented with 95% CIs for the ITT and PP populations.

The percentage of subjects surviving at 42 and 84 days after Screening/Treatment Day 1 (first dose of study drug) will be presented for the ITT and PP populations; Kaplan-Meier curves will be presented.

Safety Analyses:
All safety analyses will be conducted using the safety population; all safety variables will be listed. The incidence and severity of treatment-emergent AEs and SAEs and their relationship to treatment will be summarized. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1 or higher and presented by system organ class and preferred term.

Early discontinuation of study drug treatment will be presented and will include the reasons for and timing of such discontinuations. Prior and concomitant medications will be summarized; medications will be classified based on the World Health Organization´s Drug Dictionary terminology.

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

8.0 Schematic of Study Design

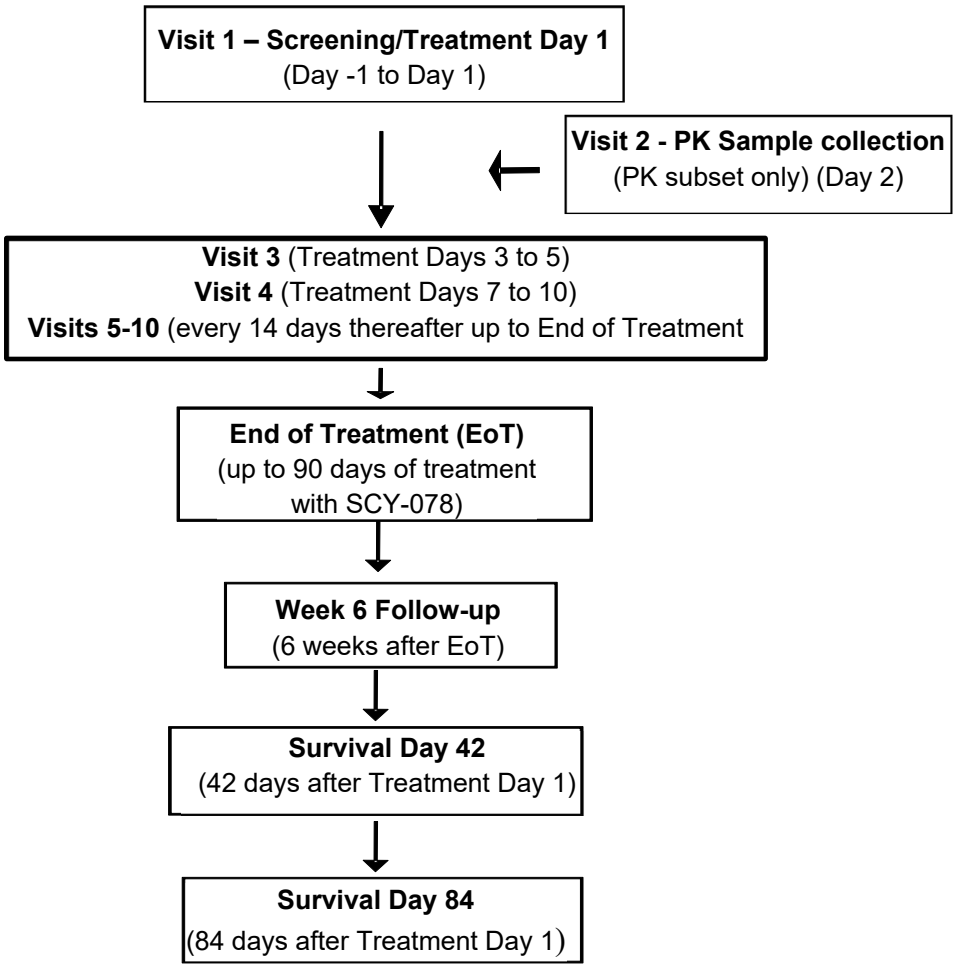

Figure 1 Schematic of Study Design

9.0 Background Information and Scientific Rationale

9.1 Background Information

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 is a member of a new class of antifungal agents and is an orally active, semi-synthetic, triterpene derivative of the natural product enfumafungin. SCY-078 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 SCY-078 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, the emergence of resistance to azoles and 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. SCY-078 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, SCY-078 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. SCY-078 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.

Activity against *Candida* spp.

SCY-078 has been evaluated against >1600 *Candida* isolates, including all clinically relevant species, more than 400 *C. glabrata* isolates and >100 *C. auris* isolates.[4,5] These *in vitro* studies have demonstrated the broad range of anti-*Candida* spectrum of activity of SCY-078. Additionally, SCY-078 demonstrated *in vitro* activity against pre-formed biofilms,[6] which is a relevant feature when addressing catheter-related *Candida* infections. Studies conducted with azole- and echinocandin-resistant strains have shown that SCY-078 retains activity (i.e., no significant change in minimum inhibitory concentration [MIC] when compared to wild type) against >90% of azole-resistant strains and >70% of *Candida* strains with *FKS* mutations commonly associated with echinocandin resistance.[7] Interestingly, although SCY-078 and the echinocandins share a similar mechanism of action (β-[1,3]-D-glucan synthesis inhibition), their clearly different molecular structure provides them with some differentiating characteristics in terms of microbiological activity.

SCY-078 was evaluated *in vitro* against >170 clinical isolates of echinocandin-resistant strains of *Candida* spp., >95% of which contained mutations in the *FKS* gene. Overall, SCY-078 was active against the majority of the echinocandin-resistant strains tested. Significantly, SCY-078 was active against approximately 70% of the isolates containing the most commonly reported *FKS* mutation associated with echinocandin resistance in *C. glabrata* (S663P in *FKS2* and S645P in *FKS1*).[7] Selection of SCY-078 resistance *in vitro* occurs at a low frequency. A deletion at position F659 in *FKS2* of *C. glabrata* was the predominant mutation observed in these studies; notably, SCY-078 did not select for mutations at positions S663 or S645.[8] These results suggest that SCY-078 inhibits glucan synthase in a manner different from that of echinocandins.

SCY-078 has also demonstrated a potent activity against life-threatening *C. auris* strains. SCY-078 has been evaluated against >100 clinical *C. auris* strains, approximately 20 of which were drug resistant.[5] SCY-078 demonstrated efficacy against both wild type (WT) and drug-resistant isolates in these studies at concentrations indicative of potential clinically relevant effect. *Candida auris* is an emerging, multi-resistant yeast that can cause invasive infections and is associated with high mortality. It is typically resistant to fluconazole and exhibits markedly variable susceptibility to other azoles, amphotericin B and echinocandins.[4,9,10] It is currently recognized to be the first exogenous candida infection. *C. auris* has been recently highlighted as a clinical alert by the Centers for Disease Control and Prevention (CDC) because of the global emergence of this fungal infection with limited therapeutic options and high mortality.

Antifungal activity

The spectrum and potency of activity of SCY-078 has been evaluated by numerous independent laboratories against an extensive panel of clinically relevant yeast and mold isolates using the Clinical and Laboratory Standards Institute (M27-A3 guidelines)[4,11] and European Committee on Antimicrobial Susceptibility Testing (EUCAST) methods. Overall, the epidemiological studies have demonstrated that SCY-078 has potent, broad-spectrum activity against the majority of the clinical isolates tested. These studies have laid the foundation in support of the use of SCY-078 for the treatment of invasive fungal infections.

Murine models of invasive fungal infections

The antifungal efficacy of SCY-078 has been evaluated in several murine models of disseminated candidiasis and aspergillosis. In a disseminated *C. albicans* model, SCY-078 was more active than fluconazole at all doses. Murine models of SCY-078 in disseminated candidiasis caused by *C. glabrata* and *C. tropicalis* indicated activity across multiple *Candida* species. The SCY-078 area under the curve (AUC) in plasma necessary to achieve target efficacy in these models was estimated to be 15.4 ± 2.2 μM•hr. Also, in an invasive murine model for *C. auris*, dose-related improvements in survival and reductions in kidney fungal burden were observed.

In a murine model of disseminated *A. fumigatus* infection that evaluated both WT and azole-resistant strains, treatment with SCY-078 resulted in improved survival and significant decreases in kidney fungal burden at all doses. The exposure needed to achieve efficacy is in line with efficacious exposures reported in the invasive candidiasis models.

The data available from all of the *in vitro* and *in vivo* studies conducted to date provide significant support for the use of SCY-078 in the treatment of invasive fungal infections.

Nonclinical experience

Toxicology studies in rats and dogs have been conducted with the oral formulation of SCY-078 administered for up to 90 days. The results from these studies indicate that SCY-078 is well tolerated and support the doses and treatment duration intended in this study.

The *in vitro* studies indicated that SCY-078 metabolism was predominantly oxidative, with cytochrome P450 (CYP) 3A being the primary enzyme involved in its oxidative metabolism. Strong inhibitors of CYP3A would be expected to increase plasma levels of SCY-078; therefore, the concurrent administration of SCY-078 with such inhibitors should be avoided.

Clinical experience

To date, over 300 subjects and patients have received either oral or IV formulations of SCY-078 in Phase 1 and Phase 2 studies.

SCY-078 was generally well tolerated following single oral doses of up to 1600 mg and multiple oral doses of up to 800 mg/day for 28 consecutive days in Phase 1 studies. Reported adverse events (AEs) after oral administration have been generally transient and primarily mild to moderate in intensity. The most frequently reported AEs have been mild gastrointestinal events (nausea, vomiting, diarrhea and abdominal pain).

A Phase 2 study of oral SCY-078 as step-down therapy from IV echinocandin in patients with invasive candidiasis has been completed. This was a multicenter, randomized, open-label study in which, following three to ten days of IV echinocandin therapy, 21 patients received either SCY-078 500 mg once daily (QD) with a 1000 mg loading dose (6 patients), SCY-078 750 mg QD with a 1250 mg loading dose (7 patients) or standard of care (SOC) treatment (8 patients with either oral fluconazole 400 mg QD with an 800 mg loading dose or IV micafungin 100 mg QD for up to 28 days). SCY-078 was well tolerated in this study, with an AE profile typical of this population and comparable to the SOC. The results from this study also indicated that the higher dose of SCY-078 tested (750 mg QD) is predicted to achieve the target exposure at steady state in the majority of patients.

A Phase 2 proof-of-concept study of oral SCY-078 in patients with vulvovaginal candidiasis (VVC) has also been completed. In this multicenter, randomized, active-controlled, evaluator-blinded study of oral SCY-078 compared to oral fluconazole in adult female patients with VVC, 96 patients with an acute, moderate to severe, symptomatic episode of VVC were randomized in a 1:1:1 ratio to receive either oral SCY-078 750 mg with a 1250 mg loading dose for three days, oral SCY-078 750 mg with a 1250 mg loading dose for five days or a single dose of oral fluconazole. SCY-078 was well tolerated, with the most common AEs being mild gastrointestinal events. The high clinical cure rates observed in this study are supportive of the clinically relevant antifungal activity of SCY-078 in this form of *Candida* infection.

Several drug-drug interaction studies have been conducted. Ketoconazole (a strong inhibitor of CYP3A) induces a significant (5-fold) increase in SCY-078 exposure, while diltiazem (a moderate inhibitor of CYP3A) induces a mild to moderate (<3 fold) increase in SCY-078 exposure. SCY-078 did not have any effect on rosiglitazone (a CYP2C8 substrate) exposure, had only a mild effect (less than a 0.5-fold increase) on the AUC of tacrolimus (a CYP3A and P-gp substrate) and had no effect on the maximum concentration (C_{max}) of tacrolimus.

SCY-078 has the potential to be an important addition to the anti-fungal treatment arsenal by providing potent activity against the full spectrum of *Candida* species, including difficult-to-treat organisms, and by affording the added flexibility of both oral and IV formulations.

For additional information on SCY-078, please refer to the Investigator´s Brochure (IB).

9.2 Rationale for the Study

This study is being conducted to evaluate the efficacy, safety, tolerability and PK (for a subset of subjects) of SCY-078 in male and female subjects ≥18 years of age with a documented *Candida auris* infection.

The primary efficacy endpoint of the study is global success, defined as either a complete or partial global (clinical and mycological) response. The primary endpoint will be determined at the end of treatment (EoT).[12,13] Clinical response will be evaluated by the signs and symptoms of the infection and/or imaging scans, if applicable. Mycological response will be assessed by fungal culture and serological testing (β-(1,3)-D-glucan),[14] if applicable. Recurrence will be assessed 42 days after the EoT (Week 6 Follow-up) as a secondary efficacy endpoint. Recurrence is defined as global success at EoT but re-emergence of the baseline *Candida* infection (with the same *Candida* species and involving the same site) during the post treatment follow-up.[13]

10.0 Study Objectives

10.1 Primary Objectives

- To evaluate the efficacy of SCY-078 as determined by a Data Monitoring Committee (DMC) by assessing global success (composite assessment of clinical and mycological success) at End of Treatment (EoT).

10.2 Secondary Objectives

- To evaluate the safety and tolerability of SCY-078
- To evaluate the efficacy of SCY-078 by measuring recurrence of the baseline fungal infection 42 days after EoT (Week 6 Follow up)
- To determine the efficacy of SCY-078 by measuring subject survival 42 and 84 days after Day 1 (first dose of study drug)

10.3 Exploratory Objectives

- To evaluate the efficacy of SCY-078 as determined by the DMC by assessing additional efficacy outcomes at EoT
- To evaluate the efficacy of SCY-078 as determined by the investigator by assessing select efficacy outcomes at EoT
- To determine the interpretative breakpoint of SCY-078 against *C. auris*
- To evaluate the pharmacokinetics (PK) of SCY-078 by population PK analysis (for a subset of subjects)

11.0 Study Endpoints

11.1 Primary Endpoints

- Efficacy as measured by the percentage of subjects with global success (complete or partial global response) at EoT as determined by the DMC

11.2 Secondary Endpoints

Safety and tolerability as measured by:

- Physical examination, vital signs, 12-lead electrocardiogram (ECG), safety laboratory tests, AEs and treatment discontinuations
- The percentage of subjects with treatment-emergent AEs

Efficacy as measured by:

- The percentage of subjects with a recurrence of the baseline fungal infection 42 days after EoT (Week 6 Follow up)
- The percentage of subjects surviving 42 and 84 days after Day 1 (first dose of study drug)

11.3 Exploratory Endpoints

- Percentage of subjects with complete global response at EoT, as determined by the DMC
- Percentage of subjects with partial global response at EoT, as determined by the DMC
- Percentage of subjects with stable disease at EoT, as determined by the DMC
- Percentage of subjects with progressive disease at EoT, as determined by the DMC
- Percentage of subjects with clinical success at EoT, as determined by the investigator
- Percentage of subjects with mycological success at EoT, as determined by the investigator
- Percentage of subjects with global success at EoT, as determined by the investigator
- Analysis of response by minimum inhibitory concentration (MIC) based on CLSI M27-A3 *in vitro* method
- SCY-078 plasma concentration by population PK analysis (for a subset of subjects)

12.0 Study Design

12.1 Overall Description of the Study

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 SCY-078 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.

Eligible 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.

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).

Efficacy will be assessed primarily in terms of global success (defined as a complete or partial global [clinical and mycological] response) at EoT as determined by the DMC. Secondary efficacy assessments will include recurrence (after EoT) and survival. Recurrence will be assessed by measuring recurrence of the baseline fungal infection 42 days after EoT (Week 6 FU). Survival will be determined on Day 42 and Day 84 (42 and 84 days after the Screening/Treatment Day 1 visit [first dose of study drug]). This can be an in-person visit or a phone contact, and will

document subject status only (alive or deceased). If subject is deceased, the relationship to the fungal infection will be recorded.

Complete global response, partial global response, stable disease and progressive disease at EoT as determined by the DMC will be assessed as exploratory efficacy endpoints. Global success, clinical success and mycological success at EoT as determined by the investigator will also be assessed as exploratory efficacy endpoints.

The following study procedures will be performed to assess treatment outcome: clinical signs and symptoms of candidiasis; radiological assessments including esophagoscopy and other imaging scans, as applicable (e.g., X-ray, ultrasound, CT and MRI); mycological testing (fungal cultures); and serological testing (ß-(1,3)-D glucan).

PK analyses will be performed for subjects who give their consent to participate in the PK portion of the study (the PK Subset). Blood samples will be collected on Treatment Day 2 (one sample collected anytime post dosing), Treatment Days 3 to 5 (one sample collected predose on any of these days) and Treatment Days 7 to 10 (one sample collected predose on any of these days).

Subjects will be evaluated for safety throughout the study, including parameters such as physical exam, vital signs, 12-lead ECGs, safety laboratory tests (hematology, blood chemistry and urinalysis), AEs, treatment discontinuations and concomitant medications. A final safety assessment will be conducted at the Week 6 Follow-up visit (6 weeks after the EoT).

Results from the study will be analyzed against historical SoC-treated subjects, who will be selected from literature reviews and other data resources, and be based on the 2015 Infectious Diseases Society of America guidelines for the management of candidiasis.[15]

12.2 Blinding, Randomization and Stratification

This is an open-label study. There will be no randomization or stratification for this study.

Eligible subjects must be approved by the Sponsor for enrollment.

12.3 Study Duration

Each subject is expected to complete the study within approximately 132 days.

12.4 Number of Subjects and Centers

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.

13.0 Study Population

13.1 Inclusion Criteria

Subjects must fulfill all of the following criteria to be eligible for study admission:

1. Subject is a male or female adult ≥18 years of age on the day the study informed consent form (ICF) is signed.
2. Subject has a documented candidiasis, including candidemia, caused by *Candida auris*. The subject is also eligible if he/she is receiving IV antifungal therapy for their *C. auris* infection and, in the judgment of the investigator, long-term IV antifungal therapy is not feasible or desirable due to clinical or logistical circumstances.

   A documented candidiasis, including candidemia, caused by *Candida auris* is defined as the recovery of *Candida auris* by culture of a sample obtained within the last 7 days.
3. Subject is able to tolerate medication orally or through a nasogastric (NG) tube or percutaneous endoscopic gastrostomy (PEG) tube.
4. Subject is not pregnant and is highly unlikely to become pregnant or to impregnate a partner since he/she meets at least one of the following criteria:
   a. Subject is a female subject who is not of reproductive potential and is eligible without requiring the use of contraception. A female subject who is not of reproductive potential is defined as one who: (1) has reached natural menopause (defined as 6 months of spontaneous amenorrhea with serum follicle-stimulating hormone levels in the postmenopausal range as determined by the local laboratory, or 12 months of spontaneous amenorrhea); (2) is 6 weeks´ post-surgical bilateral oophorectomy with or without hysterectomy; or (3) has undergone bilateral tubal ligation. Spontaneous amenorrhea does not include cases for which there is an underlying disease that causes amenorrhea (i.e., anorexia nervosa).
   b. Subject is a male subject who is not of reproductive potential and is eligible without requiring the use of contraception. A male subject who is not of reproductive potential is defined as one whom has undergone a successful vasectomy. A successful vasectomy is defined as (1) microscopic documentation of azoospermia, or (2) a vasectomy more than 2 years ago with no resultant pregnancy despite sexual activity post vasectomy.
   c. Subject is a male or female subject who is of reproductive potential and agrees to remain abstinent or use (or have his/her partner use) 2 acceptable methods of contraception starting from the time of consent through 28 days after the completion of study therapy. Acceptable methods of birth control are intrauterine device, condom, hormonal contraceptives and vasectomy.

It is not yet known if the use of SCY-078 reduces the efficacy of hormonal contraception (including but not limited to oral, injectable, or implantable methods). Therefore, hormonal contraception should not be used without a second study acceptable method of birth control.

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

5. Subject and/or legal representative is/are able to understand and sign a written ICF, which must be obtained prior to treatment and any study-related procedures.
6. Subject and/or legal representative is able to understand and sign a consent or authorization form, which shall permit the use, disclosure and transfer of the subject's personal health information (e.g., in the US, a Health Information Portability and Accountability Act Authorization form).
7. Subject and/or legal representative is able to understand and follow all study-related procedures including study drug administration.

13.2 Exclusion Criteria

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

1. Subject has a fungal disease with central nervous system involvement.
2. Subject has a fungal disease of the bone and/or joint that is expected to require >90 days of study drug treatment.
3. Subject has an inappropriately controlled fungal infection source (e.g. persistent catheters, devices, identified abscess) that is likely the source of the fungal infection.
4. Subject is hemodynamically unstable and/or requiring vasopressor medication for blood pressure support.
5. Subject has abnormal liver test parameters: AST or ALT >10 x ULN and/or total bilirubin >5 x ULN.

   Note: Subjects with unconjugated hyperbilirubinemia with diagnosis of Gilbert's disease **are not** excluded.
6. Subject has an Apache score >16.
7. Subject has serum creatinine >3 times from Baseline (Screening/Treatment Day 1) value.

8. Subject has a prolonged QTcF interval (Fridericia's correction: QTc = QT/(RR)$^{0.33}$) >480 ms on the baseline ECG or other abnormalities deemed clinically significant by the investigator that would put the subject at unacceptable risk for participation in the study.
9. Subject requires treatment with the prohibited medications listed in Section 23.1 (Appendix A), during the following timeframes:
    a. Select strong time-dependent CYP3A4/5 inhibitors and CYP3A4/5 inducers during the 14 days prior to enrollment and during study treatment
    b. Select strong and moderate reversible CYP3A4/5 inhibitors during the 48 hours prior to enrollment and during study treatment
    c. Select P-gp substrates during the 48 hours prior to enrollment and during study treatment
10. Subject is pregnant or lactating.
11. Subject has any other condition or laboratory abnormality that, in the judgment of the investigator, would put the subject at unacceptable risk for participation in the study or may interfere with the assessments included in the study.
12. Subject has a known hypersensitivity to SCY-078 or any of the components of the formulation.
13. Subject has participated in any other investigational study within at least 30 days (or 5.5 half-lives of the investigational product) before signing the ICF.
14. Subject has received prior treatment with the study drug in a previous trial.
15. Subject is an employee of SCYNEXIS, Inc., the investigator or the Contract Research Organization (CRO) involved in the study, or is an immediate family member (partner, offspring, parent, sibling, or sibling's offspring) of an employee involved in the study.
16. Subject or legal representative is unable to provide written informed consent for any reason.
17. Subject is unlikely to comply with protocol requirements.

13.3 Discontinuation Criteria

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

- Withdrawal of consent;
- Investigator or Sponsor decision that withdrawal is in the subject's best interest;
- Deterioration of the clinical condition or delayed response requiring, in the opinion of the investigator, alternative therapy.
- Occurrence of an AE that, in the opinion of the investigator, warrants discontinuation of the subject from the study drug;
- Pregnancy;

- Lost to follow up (every attempt should be made to contact the subject).

The reason for a subject's discontinuation of treatment or withdrawal from the study will be clearly documented in the source documents and on the electronic case report form (eCRF). All EoT procedures should be performed for subjects who discontinue from study treatment before the EoT visit.

13.4 Replacement of Dropouts

Subjects who discontinue early from treatment will not be replaced.

14.0 Study Treatments

14.1 Study Treatment Groups

This is an open-label, single-arm study. 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.

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.

14.2 Dietary Requirements

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

Subjects who are not hospitalized or are hospitalized and then discharged will be instructed to take the study medication in the morning upon arising and in the evening, approximately 12 hours apart (for Day 1 and Day 2). For Day 3 onwards, subjects will be instructed to take the study medication in the morning upon arising only. Subjects must take the study drug with approximately 8 oz./240 mL of water in all cases. Nutraceuticals and foods that are known CYP3A inhibitors,

such as grapefruit juice, blood oranges and mulberry juice should not be consumed during the study (see Section 23.1 [Appendix A]).

14.3 Study Drugs

The study drug, SCY-078 250-mg tablets, will be provided by the Sponsor.

14.3.1 SCY-078 Description

Study Drug Identifier: SCY-078

Empirical Formula: $C_{50}H_{75}N_5O_{11}$ (citrate salt)

Molecular Weight: 922.18 (citrate salt)

Physical Description: White to off-white solid

Chemical Name: (1S,4aR,6aS,7R,8R,10aR,10bR,12aR,14R,15R)-15-[[(2R)-2-amino-2,3,3-trimethylbutyl]oxy]-8-[(1R)-1,2-dimethylpropyl]-14-[5-(4-pyridinyl)-1H-1,2,4-triazol-1-yl]-1,6,6a,7,8,9,10,10a,10b,11,12,12a-dodecahydro-1,6a,8,10a-tetramethyl-4H-1,4a-propano-2H-phenanthro[1,2-c]pyran-7-carboxylic acid, citrate salt]

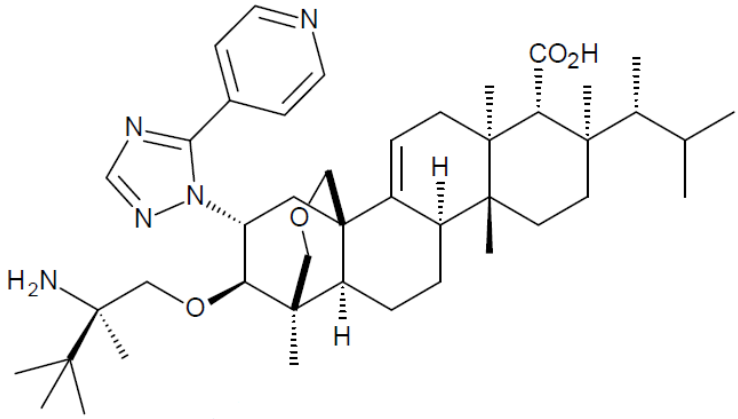

Figure 2 Chemical Structure of SCY-078 Citrate

14.3.2 Formulation, Packaging and Labelling

SCY-078 citrate drug product for oral administration will be supplied as a tablet containing 250 mg of SCY-078 active ingredient on a free-base basis. In addition to the active ingredient, the tablet formulation also contains silicified microcrystalline cellulose, crospovidone, mannitol, colloidal silicon dioxide, magnesium stearate (non-bovine) and butylated hydroxyanisole.

Study drug supplies will be packaged in bottles. Labels on the bottles of SCY-078 will include the following information:

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

14.3.3 Storage and Stability

The pharmacist or appropriate designee at each clinical research site will be responsible for the study drug. For long-term storage at the site, study drug supplies provided in bottles must be kept in a secure area (e.g., locked cabinet) and stored at room temperature, between 15°C and 30°C.

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

14.4 Drug Accountability

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

Drug supplies will be maintained in a secure, limited-access storage area under the recommended storage conditions (see Section 14.3.3).

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

This is an open-label study. A study site designee (e.g. pharmacist, study nurse/coordinator) will:

- Record the treatment in the appropriate drug accountability log
- Count the number of tablets per bottle before dispensing to the subject
- Report and document any study medication issues such as crushed or broken tablets
    - All product quality complaints should be reported to the Sponsor
- Collect and count the number of tablets remaining at the EoT visit
- Review subject diary and tablet count, record any unused or remaining drug in the drug accountability log and eCRF, and note any discrepancies and reason for discrepancies

14.5 Subject Compliance with Study Drug Dosing

Subjects who are not hospitalized and subjects who are discharged from the hospital will be instructed to have the study medication (including empty bottles/units) with them at each visit. Compliance will be assessed based on remaining study drug as compared to what should have been taken and the subject diary where the subject will enter the details of dosing. Details of treatment including any missing dose will be recorded in the eCRF. Sites are encouraged to contact the medical monitor or Sponsor for concerns of compliance with the treatment regimen, especially for subjects who miss doses due to problems with tolerability.

15.0 Non-Study Treatments

15.1 Prior and Concomitant Medications

All medications (including prescription and OTC medications, supplements, and herbal products) taken from 28 days before Screening/Treatment Day 1 through the 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.

Certain concomitant medications must be administered with caution or close monitoring as described in Section 15.2 and Section 15.3.

15.2 Prohibited Medications

Medications specifically not permitted prior to the study and through the Week-6 Follow-up visit include the following:

- Other investigational drug(s)
- Other antifungals
- Select strong CYP3A4/5 inhibitors, select moderate CYP3A4/5 inhibitors, select CYP3A4/5 inducers, and select P-gp substrates.

A detailed list of prohibited medications and timeframes is provided in Section 23.1 (Appendix A).

15.3 Medications to be Administered with Caution and Monitored as Appropriate

The following medications must be administered with caution and must be monitored as appropriate:

- Select moderate CYP3A4/5 inhibitors
- Select CYP3A4 substrates, including but not limited to sirolimus, tacrolimus and warfarin

A detailed list of medications to be administered with caution is provided in Section 23.1 (Appendix A).

15.4 Study Restrictions

There are no additional study restrictions other than those described in Sections 13.2 (Exclusion Criteria), Section 14.2 (Dietary Requirements) and Section 15.2 (Prohibited Medications).

16.0 Study Procedures

The following sections provide a description of the individual study procedures to be performed during the conduct of the study. Detailed schedules of study assessments are provided in the Schedule of Visits and Procedures in Table 1.

16.1 Informed Consent

Every study subject (or the subject´s legal representative) must provide written informed consent at Screening/Treatment Day 1, prior to participating in any Screening evaluations or any other study activities (see Section 21.3).

16.2 Inclusion and Exclusion Criteria

All inclusion and exclusion criteria will be reviewed at Screening/Treatment Day 1 (prior to study treatment) to ensure that the subject qualifies for the trial.

16.3 Subject Enrollment and Assignment of Subject Number

At Screening/Treatment Day 1, all subjects who have signed an ICF will receive an 8-digit subject identification (ID) number (prior to study treatment) that will be composed of a 3-digit study number (305) and a 2-digit site number followed by a 3-digit sequentially assigned subject number starting at 001. Subject numbers will be sequentially assigned by the database upon entry by the site. For instance, if site 01 enters the first subject in the database, the subject ID will be 305-01-001. The second subject entered in the database will get the subject number 002 as entered by any site, so that if site 02 enters the second subject, the subject ID will be 305-02-002. This number will be unique to each subject and will be used to identify the subject throughout the study.

Subjects who are screen failures or who are not eligible for enrolment will be recorded as such in the subject screening log. The subject numbers assigned to eligible subjects will be recorded in the eCRF. Only one subject number will be assigned to each eligible subject.

For subjects who signed an ICF (i.e., are assigned a subject number) but were NOT treated because they did not meet all of the inclusion/exclusion criteria, the Screening/Treatment Day 1 visit pages of the eCRF will be completed. The criteria that were not met for enrolment will be documented in the eCRF.

All eligible subjects must be approved by the Sponsor for enrollment.

16.4 Medical History and Demographics

During the Screening/Treatment Day 1 visit (prior to study treatment), a complete medical history for the prior year will be recorded for each subject. The medical history will include previous and current medical diagnoses, as well as major surgical procedures. Subject demographics such as age, sex, race and ethnicity will also be collected.

16.5 General Physical Examination

A general physical exam will be done at Screening/Treatment Day 1 (prior to study treatment), at EoT and at the Week-6 Follow-up visit. The physical examination will include an abbreviated assessment of general appearance, skin, eyes, heart, chest and abdomen.

16.6 Vital Signs

Vital signs, including blood pressure (systolic and diastolic), heart rate, respiratory rate and body temperature will be measured at Screening/Treatment Day 1 (prior to study treatment), at EoT and at unscheduled visits, if applicable.

16.7 Twelve-Lead Electrocardiogram

A 12-lead ECG will be obtained and evaluated locally by a physician for the presence of abnormalities at Screening/Treatment Day 1 (prior to study treatment), at EoT and at unscheduled visits, if applicable.

Heart rate, PR interval, QRS, QT and QTcF values will be recorded in the eCRF. Any clinically relevant abnormality will be recorded as AE accordingly and will be followed up to resolution/satisfaction.

16.8 Pregnancy Test

A serum pregnancy test will be performed at Screening/Treatment Day 1 (prior to study treatment) and at EoT by the local laboratory for all female subjects of childbearing potential.

16.9 Targeted Physical Examination, Including Clinical Evaluation of Signs and Symptoms of Infection

A targeted examination of the fungal infection site, including the signs and symptoms of the fungal disease, will be conducted at Screening/Treatment Day 1 (prior to study treatment), Treatment Days 3 to 5, Treatment Days 7 to 10, every 14 days thereafter up to EoT, at EoT, and at the Week 6 Follow-up.

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

- Fever, defined as oral temperature ≥38.3°C (≥101°F) on one occasion or >37.8°C (>100°F) on two measurements at least 4 hours apart
- Clinically significant hypothermia <36°C (<96.8°F)
- Hypotension (systolic blood pressure <90 mmHg or a >30 mmHg decrease below normal baseline)
- Tachycardia

Subjects who are discharged from the hospital during SCY-078 therapy will record signs and symptoms daily on subject diaries and the signs and symptoms will also be assessed by the site staff at the study visits. The site will assess whether the signs and symptoms recorded on the subject diary are related to the *C. auris* infection.

16.10 Mycological Testing

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

Non-blood cultures: A documented culture positive for *C. auris* of a sample obtained within the last 7 days must be available at Screening/Treatment Day 1 (prior to study treatment). Follow-up cultures from subjects who have non-blood *Candida auris* infections should be performed as clinically indicated.

The study site's local microbiology laboratory will perform identification and *in vitro* susceptibility testing as per their local standards. The investigator should ensure that all *Candida auris* isolates obtained from all cultures performed during the study period are sent to the central microbiology laboratory, as described in the laboratory manual.

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

16.11 Imaging

Imaging scans (e.g., X-ray, ultrasound, computed tomography, magnetic resonance imaging) should be performed for the assessment of infection in subjects with non-blood sites of *Candida* infection. The results of these studies should be documented on the eCRF.

For subjects with fungal diseases where the assessment of outcome is based on imaging, imaging scans must be available at Screening/Treatment Day 1 (prior to study treatment) and performed at EoT. Additional images should be obtained if clinically indicated.

16.12 Serological Testing

The following serological examinations will be performed at Screening/Treatment Day 1 (prior to study treatment) and at the recommended time points below:

- Two ß-(1,3)-D-glucan consecutive tests every 72 hours until negative

16.13 Safety Laboratory Tests

Safety laboratory tests (hematology, blood chemistry and urinalysis) will be measured at Screening/Treatment Day 1 (prior to study treatment), at Treatment Days 7 to 10, every 14 days

thereafter up to EoT if clinically indicated, at EoT, at the Week 6 Follow-up if clinically indicated, and at unscheduled visits if clinically indicated. These may also be done more frequently as follow up to a laboratory abnormality.

The following laboratory parameters will be determined:

Hematology

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

Blood Chemistry

- Sodium
- Potassium
- Alkaline Phosphatase
- Chloride
- Blood urea nitrogen (BUN)
- Creatinine
- Total creatine phosphokinase (CPK)
- Aspartate aminotransferase (AST/SGOT)
- Alanine aminotransferase (ALT/SGPT)
- Gamma glutamyl transferase (GGT)
- Lactate dehydrogenase (LDH)
- Bilirubin (total, direct, and indirect)
- Total protein
- Glucose
- Albumin

Coagulation test

- Prothrombin time (PT)
- Activated partial thromboplastin (aPTT)
- Thrombin time (TT)
- D-dimer

Urinalysis

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

Reflex Microscopic Evaluation

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

16.14 Pharmacokinetic Sample Collection (PK Subset Only)

PK testing will be conducted for subjects who give their consent to participate in the PK portion of the study (the PK Subset). Up to three (3) blood samples will be collected at the following visits and sampling windows: Treatment Day 2 (one sample collected anytime post dosing), Treatment Days 3 to 5 (one sample collected predose on any of these days) and Treatment Days 7 to 10 (one sample collected predose on any of these days).

On PK sampling days, the investigator must record the dosing times and sample collection times on the eCRF and on the subject's medical record.

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

Further analysis of possible metabolites may be performed.

16.15 Efficacy Assessment

Efficacy will be assessed primarily in terms of global success at EoT as determined by the DMC. Complete global response, partial global response, stable disease and progressive disease as determined by the DMC and global success, clinical success and mycological success as determined by the investigator will also be assessed at EoT.

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

- Clinical signs and symptoms of candidiasis (Section 16.9)
- Radiological assessments including esophagoscopy and other imaging scans, as applicable (e.g., X-ray, ultrasound, CT and MRI) (Section 16.11).
- Mycological testing (fungal cultures) (Section 16.10.)
- Serological testing (ß-(1,3)-D glucan) (Section 16.12)

Efficacy assessments will also include recurrence (after EoT) and survival. Recurrence will be assessed by measuring recurrence of the baseline fungal infection 42 days after EoT (Week 6 FU). Survival will be determined on Day 42 and Day 84 (42 and 84 days after Screening/Treatment Day 1 [first dose of study drug]). This can be an in-person visit or a phone contact, and will document subject status only (alive or deceased). If subject is deceased, the relationship to the fungal infection will be recorded.

See Section 20.7.1 for a detailed description of efficacy outcomes.

16.16 Study Drug Dispensing, Collection and Treatment Compliance Evaluation

For subjects who are not hospitalized, the study drug will be dispensed at Screening/Treatment Day 1. Subjects who are hospitalized and are later discharged from hospital will be dispensed their study drug at the time they are discharged. Study drug will be dispensed at each Treatment visit and will be supplied in bottles containing enough study drug to last until the next study visit. Study drug will be collected for treatment compliance evaluation on Treatment Days 3 to 5, Treatment Days 7 to 10, every 14 days thereafter up to EoT and at unscheduled visits prior to EoT (see **Section 14.5** for further details).

16.17 Study Drug Dosing

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. 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.

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.

Further details of the study treatment and dietary requirements for treatment administration are provided in Section 14.1 and Section 14.2, respectively.

16.18 Subject Diary Dispensing, Collection and Review

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

Subject diaries will be dispensed at Screening/Treatment Day 1 and will be reviewed on Treatment Days 7 to 10, every 14 days thereafter up to EoT, at EoT and at any unscheduled visit conducted prior to EoT. Subject diaries will be collected at EoT.

16.19 Prior and Concomitant Medication Review

All medications (including prescription and OTC medications, supplements, and herbal products) taken from 28 days before Screening/Treatment Day 1 through the 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. See Section 15.0 for prohibited medications, medications to be administered with caution and further details for non-study treatments.

16.20 Adverse Event Monitoring

AEs will be collected and evaluated from the time the informed consent is signed through the EoT. After the EoT and up to the last observation in the study (Week 6 Follow-up), new AEs will be collected only if deemed related to the study drug, if they are serious adverse events (SAEs), or if they are related to a fungal infection.

See Section 18.0 for details regarding safety assessment and monitoring.

17.0 Study Schedule

Detailed schedules of all study visits and procedures are presented in the Schedules of 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
Adverse Event Monitoring	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	

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 2 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

18.0 Safety Assessments and Monitoring

18.1 Definition of an Adverse Event

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

Any laboratory abnormality that is deemed to be clinically significant in the opinion of the investigator will be considered an AE and should be recorded in the eCRF, whether or not it is related to the study drug.

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

The following can be considered AEs:

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event or condition
- A condition detected or diagnosed after the initiation of treatment with study medication, even though it may have been present prior to the start of the study
- Continuous persistent disease or symptoms present at Baseline that worsen after signing the informed consent or following the initiation of treatment with study medication

The following are **not** considered AEs:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction or transfusion); the condition that leads to the procedure is an AE
- Pre-existing disease or conditions present or detected at the start of the study that do not worsen
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalizations for cosmetic surgery or elective surgery or social/convenience admissions)

- The disease being studied or signs or symptoms associated with the disease, unless more severe than expected for the subject's condition or a worsening of the disease being studied

18.2 Definition of a Serious Adverse Event

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

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

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

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

18.3 Events of Clinical Interest

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

- QTc >500 ms or a >60-ms change from Baseline, confirmed by repeat testing
- ALT or AST >8 x ULN, if new compared to Baseline, confirmed by repeat testing
- ALT or AST >5 x ULN for more than 2 weeks and if new compared to Baseline, confirmed by repeat testing
- ALT or AST >3 x ULN and either total bilirubin >2 x ULN or INR >1.5 and if new compared to Baseline, confirmed by repeat testing
- ALT or AST >3 x ULN, confirmed by repeat testing, with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)]

18.4 Overdose

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

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

18.5 Pregnancy

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

18.6 Unexpected Adverse Event

An AE is considered “unexpected” if it is not listed in the IB or is of greater specificity or severity than those that have been observed with the particular study drug being tested. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

18.7 Grading of Adverse Events

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

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

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

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

18.8 Causality Assessment

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

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

18.9 Adverse Event Collection Timeframe

AEs will be collected and evaluated from the time the informed consent is signed through the EoT. After the EoT and up to the last observation in the study, new AEs will be

collected only if deemed related to the study drug, if they are SAEs, or if they are related to a fungal infection.

All AEs reported by the subject or observed by members of the clinical staff will be evaluated by the principal investigator (PI) or qualified designee. The PI will attempt, if possible, to establish a diagnosis based on presenting signs and symptoms. The nature of the AE, time of onset relative to study drug administration, duration, severity, and relationship to treatment should be determined. Details of any corrective treatment must be recorded in the eCRF. The PI will determine whether any changes have occurred in baseline signs and symptoms. All AEs and SAEs will be collected in the eCRF.

18.10 Serious Adverse Event Reporting Requirements

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

18.11 Adverse Event and Serious Adverse Event Follow-up

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

18.12 Serious Adverse Event Reporting – Procedures for Investigators

Initial Reports and Follow-Up SAE Reports:

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

18.13 Procedures for Emergency Unblinding

This is an open-label study. No procedures for emergency unblinding are needed.

19.0 Data Collection, Study Monitoring and Record Management

19.1 Data Collection and Reporting

Data for this study will be collected using eCRFs. The investigator and study site staff will receive training regarding the completion of the eCRF. Visit-specific data should be entered into the eCRF and be ready for review as soon as possible, but no later than 5 days after each visit/time point.

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

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

19.2 Study Monitoring

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

19.3 Investigator Study Files

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

- original protocol and all amendments;
- signed agreement or protocol;
- signed and dated study staff roles and responsibilities log;
- copy of the current *curriculum vitae* of the PI and of all sub-investigators;

- IRB/EC membership list and all IRB/EC approvals for the protocol and amendments, informed consent documentation and all updates, advertisements, and written information provided to subjects; all IRB/EC correspondence; documentation that the IB and subsequent revisions have been submitted to the IRB/EC; documentation that all SAEs and any periodic safety reports have been submitted to the IRB/EC; and annual IRB/EC renewals (as required);
- updated laboratory certification and the laboratory's normal values (covering the entire time interval of the study for all laboratory tests conducted during the study);
- all confirmations of investigational drug receipt, drug accountability logs and drug return records;
- a CD or DVD containing final subject eCRF data;
- all correspondence to or from the Sponsor or its designees;
- blank informed consent form;
- Investigator's Brochure;
- subject screening log;
- subject list (contains subject initials and/or protocol-specific subject number);
- all subjects' original signed informed consents; and,
- monitoring visit log.

19.4 Retention of Records

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

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

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

20.0 Analytical Plan

All statistical processing will be performed using SAS® version 9.3 or later, unless otherwise stated.

Descriptive statistics (i.e., number of subjects, mean, standard deviation, median, minimum, maximum) will be presented for all continuous variables; number and

percentage of subjects will be presented for categorical variables. For parameters measured over time, observed data and changes from baseline will be described for each time point.

All analyses of the study results for SCY-078 will be descriptive. Unless otherwise stated, data will be analyzed as is with no imputation.

A Statistical Analysis Plan (SAP) describing all statistical analyses in detail will be provided as a separate document.

20.1 Sample Size Determination

This is an exploratory study and no formal sample size calculation was performed.

A total of 30 subjects are estimated to be adequate for an assessment of the safety and tolerability of SCY-078 in subjects with candidiasis, including candidemia, caused by *C. auris.*

20.2 Analysis Populations

Intent-to-Treat (ITT) Population: The ITT Population will include all subjects who are enrolled in the study.

Per-Protocol (PP) Population: The PP Population will include all ITT subjects who receive at least 10 total days of antifungal therapy (SCY-078), 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.

PK Population: The PK Population will include all enrolled subjects who provide at least one PK sample.

20.3 Subject Disposition, Discontinuation, and Baseline Data

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. Subject demographics and baseline characteristics such as age, race, ethnicity, sex, weight, height, body mass index, country and other relevant parameters will be tabulated.

Baseline is defined as the last non-missing assessment prior to the date (and time if appropriate) of the first dose of study drug. Change from baseline is defined as:post-baseline value – baseline value.

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

For the efficacy analyses, subjects who do not have an EoT assessment will be assigned as treatment failures. For subjects who withdraw from the study early, every effort will be made to collect EoT visit information at the point of withdrawal.

20.5 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary terminology. The number and percentage of subjects taking each medication before and after the first dose of study drug will be tabulated. Medications taken and stopped prior to the first dose of study drug will be considered prior medications. Medications started on or before the FU visit date with missing stop dates or stop dates after the first dose of study drug will be considered concomitant medications.

20.6 Pharmacokinetics (PK Subset Only)

20.6.1 Pharmacokinetic Assessments

PK testing will be conducted for subjects who give their consent to participate in the PK portion of the study (the PK Subset). Up to three (3) blood samples will be collected at the following visits and sampling windows: Treatment Day 2 (one sample collected anytime post dosing), Treatment Days 3 to 5 (one sample collected predose on any of these days), and Treatment Days 7 to 10 (one sample collected predose on any of these days).

20.6.2 Pharmacokinetic Analyses

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

20.7 Efficacy

20.7.1 Efficacy Assessments

20.7.1.1 Clinical, Mycological and Global Outcomes

Efficacy will be assessed primarily in terms of global success (defined as a complete or partial global (clinical and mycological) response) at EoT as determined by the DMC. Complete global response, partial global response, stable disease and progressive disease at EoT as determined by the DMC will be assessed as exploratory endpoints. Global success, clinical success and mycological success at EoT as determined by the investigator will also be assessed as exploratory endpoints.

Global Outcome

Global outcome will be scored as global success (complete global response or partial global response) or global failure (stable disease or progressive disease)

Global success: Global success is defined as a complete global response or a partial global response

- Complete global response is defined as a complete clinical response (the resolution of all clinical signs and symptoms and/or radiological abnormalities from baseline attributable to 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 is defined as a 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])

Global failure: Global failure is defined as either stable disease and/or progressive disease

- Stable disease is defined as minor or no clinical improvement but without deterioration and/or unchanged serological response.
- Progressive disease is defined as clinical deterioration necessitating alternative antifungal therapy or resulting in death, and/or worsened serological response, and/or persistence of fungal infection on the basis of culture, microscopic evaluation, or histopathological testing.

Clinical Outcome

Clinical success: 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 Outcome

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

20.7.1.2 Recurrence and Survival

Secondary efficacy assessments will include recurrence (after EoT) and survival.

Survival: Survival will be determined on Day 42 and Day 84 (42 and 84 days after Screening/Treatment Day 1 [first dose of study drug]). This can be an in-person visit or a phone contact, and will document subject status only (alive or deceased). If subject is deceased, the relationship to the fungal infection will be recorded.

Recurrence: Recurrence will be assessed by measuring recurrence of the baseline fungal infection 42 days after EoT (Week 6 FU).

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.

20.7.2 Efficacy Analyses

The primary efficacy endpoint, the percentage of subjects with global success (complete or partial global response) as determined by the DMC at EoT, will be presented with a 95% confidence interval (CI) for the ITT and PP populations.

Secondary and exploratory categorical endpoints will be presented with 95% CIs for the ITT and PP populations.

The percentage of subjects surviving at 42 and 84 days after Screening/Treatment Day 1 (first dose of study drug) will be presented for the ITT and PP populations; Kaplan-Meier curves will be presented.

20.8 Safety

20.8.1 Safety Assessments

Subjects will be evaluated for safety and tolerability throughout the study, including parameters such as physical exam, vital signs, 12-lead ECGs, safety laboratory tests (hematology, blood chemistry and urinalysis), concomitant medications, AEs and treatment discontinuations.

Safety procedures are described in **Section 16.0** and safety assessments are described in **Section 18.0**.

20.8.2 Safety Analyses

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

The incidence and severity of treatment-emergent AEs and SAEs and their relationship to treatment will be summarized. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1 or higher and presented by system organ class and preferred term.

Early discontinuation of study drug treatment will be presented and will include the reasons for and timing of such discontinuations.

Prior and concomitant medications will be summarized; medications will be classified based on the World Health Organization´s Drug Dictionary terminology.

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

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

21.0 Ethics and Protection of Human Patients

21.1 Ethical Conduct of the Study

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

21.2 Institutional Review Board/Ethics Committee Review

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

21.3 Informed Consent

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

21.4 Future Use of Samples

Biological samples collected during the study, including *Candida* spp. isolates (see Section 16.10) and plasma samples (see Section 16.12 and Section 16.13) may be

maintained in repositories for potential future use. Future research of samples and/or *Candida* isolates may include *in vitro* susceptibility testing of new or existing antifungals or analysis of mechanisms of resistance. Future research of plasma samples may include analysis of *in vitro* diagnostics and/or an analysis of SCY-078 metabolites. Future research may also include studies that are unknown at this time. The samples will be retained as long as deemed useful for the specified research purposes. All samples will be identified only by a coded number to maintain subject confidentiality. Researchers requesting samples or information from the repository must have a research protocol approved by an Institutional Review Board/Ethics Committee. Samples will only be retained for subjects that provide consent for future use.

21.5 Subject Privacy and Subject Confidentiality

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

21.6 Study Termination

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

21.7 Financial Disclosure

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

22.0 References

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23.0 Appendices

23.1 Appendix A: Prohibited Medications and Medications to be Administered with Caution

23.1.1 Prohibited Medications

Investigational Drugs

No other investigational drugs are allowed during the study from at least 30 days (or 5.5 half-lives) before signing the informed consent through the Week-6 Follow-up visit.

Antifungals

No antifungal treatment other than the study drug is allowed during the study.

Other Prohibited Medications

In addition, the medications listed below are also prohibited.

Strong CYP3A4/5 inhibitors, moderate CYP3A4/5 inhibitors and CYP3A4/5 inducers

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

a. The CYP3A4/5 inducers and strong time-dependent CYP3A4/5 inhibitors listed in this table are not permitted during the 14 days prior to enrollment and during study treatment.
b. The strong or moderate reversible CYP3A4/5 inhibitors listed in this table are not permitted during the 48 hours prior to enrollment and during study treatment.
c. No antifungal treatment other than the study drug is allowed during the study.

P-glycoprotein (P-gp) substrates

P-gp Drug Substrates[a]
digoxin, colchicine

a. The P-gp substrates listed in this table are not permitted during the 48 hours prior to enrollment and during study treatment.

23.1.2 Medications to be administered with Caution and Monitored as Appropriate

CYP	Moderate Inhibitors	
3A4/5	Reversible inhibitors • amprenavir • aprepitant • atazanavir • buprenorphine • ciprofloxacin • crizotinib • cyclosporine	• darunavir/ritonavir • fosamprenavir • imatinib • grapefruit juice, blood oranges, mulberry juice
	Time-dependent inhibitors: • diltiazem • erythromycin • verapamil	

CYP3A4 substrates

CYP	Substrates
3A4	In vitro, SCY-078 was an inhibitor of CYP3A mediated metabolism of midazolam, but was only a weak inhibitor of metabolism of testosterone. The clinical significance of this inhibition is unknown; caution should be exercised when administering SCY-078 with drugs known to be CYP3A sensitive substrates with narrow therapeutic index. Subjects receiving sirolimus, tacrolimus or warfarin are permitted for enrollment in the study and these medications may be administered concomitantly with SCY-078 with close monitoring. The administration of either sirolimus or tacrolimus should be offset by no less than 2 hours with the administration of SCY-078. At a minimum, blood levels of sirolimus, tacrolimus or PT/PTT/INR for subjects on warfarin should be measured after the first dose of SCY-078 and when the subject has received approximately 7 days of SCY-078 (at which time, SCY-078 concentrations will have reached steady state). Dosing adjustments and subsequent monitoring of sirolimus and warfarin should be undertaken in accordance with product prescribing information for the respective agents.

Abbreviations: PT = prothrombin time; PTT = partial thromboplastin time; INR = international normalized ratio

Sources:

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