SCYNEXIS, Inc.

Clinical Trial Protocol

A Phase 2, Multicenter, Randomized, Double-Blind, Double-Dummy, Active-Controlled, Dose-Finding Study to Compare the Safety and Efficacy of Oral SCY-078 vs. Oral Fluconazole in Subjects with Acute Vulvovaginal Candidiasis **(DOVE)**

SCYNEXIS Protocol Number SCY-078-204

SCYNEXIS, Inc.

101 Hudson Street, Suite 3610

Jersey City, NJ 07302

Original Protocol Issue Date: 08 June 2017 (Version 1.0)

Protocol Amendment 1 Issue Date: 13 Jul 2017 (Version 2.0)

NCT03253094

US IND Number 107,521

1.0 Contact Information

Contract Research Organization	[redacted]
Study Medical Monitor	[redacted]
Clinical Project Manager	[redacted]
Sponsor	SCYNEXIS, Inc. 101 Hudson Street, Suite 3610 Jersey City, NJ 07302 Phone: +1.201.884.5485 Fax: +1.201.884.5490 Email: info@scynexis.com

2.0 Protocol Approvals

PROTOCOL ID: SCY-078-204

A Phase 2, Multicenter, Randomized, Double-Blind, Double-Dummy, Active-Controlled, Dose-Finding Study to Compare the Safety and Efficacy of Oral SCY-078 vs. Oral Fluconazole in Subjects with Acute Vulvovaginal Candidiasis (DOVE)

SCYNEXIS, Inc. Approval:

[redacted]

13-July-2017
Date

[redacted]
101 Hudson Street, Suite 3610
Jersey City, NJ 07302
Phone: 201-884-5480
Fax: 201-884-5490
E-mail: silvia.helou@scynexis.com

Investigator Agreement Statement

PROTOCOL ID: SCY-078-204

A Phase 2, Multicenter, Randomized, Double-Blind, Double-Dummy, Active-Controlled, Dose-Finding Study to Compare the Safety and Efficacy of Oral SCY-078 vs. Oral Fluconazole in Subjects with Acute Vulvovaginal Candidiasis (DOVE)

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)

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

3.0 Revision History

Revisions to Protocol dated 08 Jun 2017 (Protocol Version 1.0) **Current Version and Date: Protocol Amendment 1 (Protocol Version 2.0) dated 13 Jul 2017**	
Protocol Sections	**Change and Rationale**
Section 10.1.1 (Study Visits) and Section 15.0 (Study Schedule)	Removed the option for a phone call for the FU visit to ensure collection of vaginal samples from all subjects for mycological assessment in order to accommodate the requirements of the secondary objective "percentage of subjects with both clinical cure and mycological eradication at the TOC and FU visits".
Section 14.9 (Vulvovaginal Samples for KOH and Fungal Culture), Section 15.0 (Study Schedule) and other applicable sections	Added the collection of vaginal samples for KOH testing and fungal culture at FU for all subjects to assess treatment outcome, as required by the above mentioned secondary objective.
Section 14.10 (Rating of Vulvovaginal Signs by the Investigator Using the VSS Scale) and other applicable sections	Added the rating of signs of infection by the investigator in addition to the subject´s rating of symptoms for all subjects at FU, as a result of the fact that all FU visits will be conducted face to face.
Section 7.2 (Rationale for the Study), Secondary and Exploratory Endpoints (Section 9.2 & Section 9.3), Section 10.1 (Overall Description of the Study including Section 10.1.1 & 10.1.2) and Section 18.7.1 (Efficacy Assessments)	Revised secondary and exploratory endpoints to include the assessment of both signs and symptoms at the FU visit, as a result of the fact that all FU visits will be conducted in person. Revised applicable outcome definitions to include signs of vulvovaginal infection.
Section 11.1 (Inclusion Criteria)	Clarified acceptable methods of contraception.
Section 13 (Discontinuation Criteria)	Clarified that all FU visit procedures should be done for subjects who discontinue after the TOC visit but before the FU visit.

Revisions to Protocol dated 08 Jun 2017 (Protocol Version 1.0) **Current Version and Date: Protocol Amendment 1 (Protocol Version 2.0) dated 13 Jul 2017**	
Protocol Sections	**Change and Rationale**
Section 14.6 (Urine Pregnancy Test)	Clarified that pregnancy test results will be reviewed at Baseline (Day 1) before starting/dispensing study drug.
Section 14.7 (Safety Laboratory Tests)	Removed segmented neutrophils from the list of parameters included in the differential WBC count.

4.0 Abbreviations

ABBREVIATION	DEFINITION
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-24}	area under the concentration-time curve from 0 to 24 hours
AVVC	acute vulvovaginal candidiasis
BID	twice daily
CD	compact disk
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
C_{max}	maximum concentration
CPK	creatine phosphokinase
CRO	contract research organization
CYP	cytochrome P450
DVD	digital versatile disk
EC	Ethics Committee
ECI	event of clinical interest
eCRF	electronic case report form

ABBREVIATION	DEFINITION
FDA	Food and Drug Administration
FU	follow-up
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GSI	glucan synthesis inhibitor
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
IWRS	interactive web response system
KOH	potassium hydroxide
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
OATP1B3	Organic anion-transporting polypeptide 1B3
PI	principal investigator
PK	pharmacokinetics
Pop PK	population pharmacokinetics
PP	per protocol
QD	once daily
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SGOT	serum glutamic oxaloacetic transaminase

ABBREVIATION	DEFINITION
SGPT	serum glutamic pyruvic transaminase
SOC	standard of care
TOC	test of cure
ULN	upper limit of normal
US	United States
VSS Scale	Vulvovaginal Signs and Symptoms Scale
WBC	white blood cell

5.0 Protocol Synopsis

Title: A Phase 2, Multicenter, Randomized, Double-Blind, Double-Dummy, Active-Controlled, Dose-Finding Study to Compare the Safety and Efficacy of Oral SCY-078 vs. Oral Fluconazole in Subjects with Acute Vulvovaginal Candidiasis (DOVE)

Primary Objectives:

- To identify the recommended dose of oral SCY-078 in subjects with moderate to severe acute vulvovaginal candidiasis (AVVC) by comparing the efficacy of different dose levels and dosing regimens of oral SCY-078

Secondary Objectives:

- To evaluate the efficacy of oral SCY-078 in subjects with AVVC based on mycological and clinical outcomes
- To evaluate the safety and tolerability of different dose levels and dosing regimens of oral SCY-078 in subjects with AVVC

Exploratory Objectives:

- To explore the efficacy of SCY-078 in subjects with AVVC based on potassium hydroxide (KOH) testing at the TOC visit
- To explore the efficacy of SCY-078 in subjects with AVVC based on additional clinical outcomes
- To explore the prevalence of *Candida* species among subjects with AVVC
- To explore the *in vitro* activity of SCY-078 against baseline *Candida* spp. isolates
- To explore clinical and mycological outcomes by *Candida* species
- To evaluate the pharmacokinetics (PK) of SCY-078 after oral administration of different dose levels and dosing regimens in subjects with AVVC

Primary Endpoints:

- Efficacy as measured by the percentage of subjects with clinical cure (complete resolution of signs and symptoms) at the test-of-cure (TOC) visit

Secondary Endpoints:

Efficacy as measured by:

- The percentage of subjects with mycological eradication (negative fungal culture) at the TOC visit
- The percentage of subjects with both clinical cure and mycological eradication at the TOC and Follow-up (FU) visits.
- The percentage of subjects with continued clinical response cure (continued absence of signs and symptoms) at the FU visit.
- The time to resolution of signs and symptoms after initiation of study drug

Safety and tolerability as measured by:

- AEs, treatment discontinuations, vital signs, physical examination and safety laboratory tests

Exploratory Endpoints:

- Percentage of subjects with a negative KOH test at the TOC visit
- Percentage of subjects who are free of signs and symptoms at the FU visit.
- Percentage of subjects by *Candida* species infection at Baseline
- Percentage of isolates susceptible to SCY-078 and fluconazole
- Percentage of subjects with clinical cure (complete resolution of signs and symptoms) at TOC by *Candida* species
- Percentage of subjects with mycological eradication (negative fungal culture) at TOC by *Candida* species
- Determination of the PK parameters (maximum concentration [C_{max}] and area under the concentration-time curve [AUC]) for each dosing regimen and evaluation of the dose/exposure relationship relative to clinical outcome

Study Phase: Phase 2

Study Design:

This is a multicenter, randomized, double-blind, double-dummy, active-controlled, dose-finding study to compare the efficacy, safety and tolerability of oral SCY-078 compared to oral fluconazole in adult female subjects 18 years and older with moderate to severe AVVC. Approximately 180 eligible subjects (30 subjects per treatment group) will be enrolled and randomized into the study.

The primary objective of this study is to identify the recommended dose of oral SCY-078 in subjects with moderate to severe AVVC by comparing the efficacy of different dose levels and dosing regimens of SCY-078.

The study will consist of a Screening visit, a Baseline visit on Day 1, a study visit on Day 3

(which will consist of an on-site visit for PK sampling for a subset of subjects and a phone contact for all other subjects), a TOC visit (which will include PK sampling for the PK Subset of subjects) on Day 10 (±2) and a FU visit on Day 25 (+4). The Screening and Baseline visits may be combined. Efficacy, safety, tolerability and PK assessments will be conducted for the study.

Efficacy will be determined primarily by the percentage of subjects with clinical cure (complete resolution of signs and symptoms) at the TOC visit. Secondary efficacy endpoints will include mycological eradication (negative fungal culture) at the TOC visit, a composite endpoint of both clinical cure and mycological eradication at the TOC and FU visits, continued clinical response cure (continued absence of signs and symptoms) at the FU visit, and time to resolution of signs and symptoms after initiation of study drug. Other efficacy endpoints will also be explored. Safety and tolerability will be evaluated throughout the study, including the following parameters: physical exam, vital signs, adverse events (AEs), treatment discontinuations, and safety laboratory tests. A subset of approximately 60 subjects will also undergo blood sampling for PK analyses of SCY-078 in plasma.

At Screening, subjects who are experiencing vulvovaginal symptoms will be evaluated by the investigator, who will obtain a vaginal sample for local KOH testing and for fungal culture and species identification by the central laboratory. Susceptibility testing will be done at the central laboratory for all positive cultures for *Candida* spp. Additional vaginal samples will be collected, if clinically indicated, to be examined for the presence of other pathogens (e.g., causative agents for bacterial vaginosis, *Trichomonas*, *Herpes* virus, *N. gonorrhea*, *Chlamydia*, human papillomavirus or other mixed infections) by a qualified laboratory and for the determination of vaginal pH by the investigator. The investigators and the subjects will rate the signs (edema, erythema and excoriation) and symptoms (itching, burning and irritation) of infection, respectively, on a standardized vulvovaginal signs and symptoms scale (the Vulvovaginal Signs and Symptoms [VSS] Scale). Safety procedures, including an abbreviated physical exam, vital signs, laboratory tests and a pregnancy test will also be performed. To be eligible for inclusion, subjects must have a minimum composite score of vulvovaginal signs and symptoms ≥7 with at least 2 signs or symptoms having a score of 2 (moderate) or greater in the VSS Scale, a positive KOH test and a normal vaginal pH (≤4.5).

At the Baseline visit (which may be combined with the Screening visit), eligible subjects will be randomized in equal allocation (at a 1:1:1:1:1:1 ratio) to one of the following 6 active treatment groups (5 experimental groups and 1 active comparator group):

- Treatment Group 1: oral SCY-078 750 mg QD on Day 1 only
- Treatment Group 2: oral SCY-078 300 mg BID on Day 1 only
- Treatment Group 3: oral SCY-078 450 mg BID on Day 1 only
- Treatment Group 4: oral SCY-078 150 mg BID on Days 1 to 3
- Treatment Group 5: oral SCY-078 300 mg BID on Days 1 to 3
- Treatment Group 6: oral fluconazole 150 mg QD on Day 1 only

Subjects will receive randomized treatment from Day 1 through Day 3. For the purpose of maintaining treatment blinding, all randomized subjects will receive matching SCY-078 placebo tablets and/or matching fluconazole placebo capsules as needed based on treatment assignment, in a double-dummy fashion. During treatment days, subjects will rate their vulvovaginal symptoms and record dosing details, AEs and concomitant medication use daily on subject diaries. On Day 3, a PK Subset consisting of 10 subjects per treatment group (total of 60 subjects) will visit the site to have PK samples drawn pre-dose (immediately before dosing) and at 2-6 hours' post-dose of either the morning or evening dose. Day 3 will be an on-site visit for PK

subjects and a phone contact visit (with a window of +3 days) for non-PK subjects. All subjects (both PK and non-PK subjects) will continue to take their assigned study treatment and rate their symptoms of infection within their subject diaries. Treatment compliance will be reviewed either on site or by phone for all subjects. Study drug may be collected from PK subjects who have completed study drug dosing at the time of this visit.

At the TOC visit (Day 10 [±2]) vaginal samples will be obtained for local KOH testing and for fungal culture by the central laboratory. In addition, susceptibility testing will be done at the central laboratory for all positive cultures for *Candida* spp. The investigators and the subjects will rate the signs and symptoms of infection, respectively, on the VSS Scale. An abbreviated physical exam, vital sign measurements and safety laboratory tests will also be performed. Additionally, a single PK sample will be obtained at any convenient time of the day from the PK Subset only. For the PK Subset, the TOC visit must occur as close to Day 10 as possible. All subjects will return their subject diaries. Compliance with study drug dosing will be evaluated and study drug will be collected for all subjects who did not return their study drug on Day 3.

At the FU (Day 25[+4])) visit, vaginal samples will be obtained for local KOH testing and for fungal culture by the central laboratory. In addition, susceptibility testing will be done at the central laboratory for all positive cultures for *Candida* spp. The investigators and the subjects will rate the signs and symptoms of infection, respectively, on the VSS Scale to evaluate clinical outcome.

AEs and prior/concomitant medications will be assessed and documented at all visits.

Target Population: Adult female subjects 18 years and older, with moderate to severe AVVC

KEY Inclusion Criteria

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

1. Subject is a female subject 18 years and older and is in good general health based on medical history, physical examination, vital sign measurements and safety laboratory tests performed at the Screening visit and/or prior to administration of the initial dose of study drug.
2. Subject has a diagnosis of symptomatic AVVC that meets the following criteria:
    a. Moderate to severe disease, defined as a minimum composite vulvovaginal signs and symptoms score of ≥7 with at least 2 signs or symptoms having a score of 2 (moderate) or greater in the VSS Scale at Baseline
    b. Positive microscopic examination with 10% KOH in a vaginal sample collected at Screening revealing yeast forms (hyphae/pseudohyphae) or budding yeasts
    c. Normal vaginal pH (≤4.5)

KEY Exclusion Criteria

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

1. Subject has any vaginal condition other than AVVC that may interfere with the diagnosis or evaluation of response to therapy, such as suspected or confirmed concurrent causes of vulvovaginitis and/or cervicitis including bacterial vaginosis, *Trichomonas*, active *Herpes* virus, *N. gonorrhea*, *Chlamydia*, active human papillomavirus or other mixed infections.

2. Subject requires treatment with the prohibited medications (including prescription and over-the-counter medications, supplements, and herbal products) listed in Section 21.0 (Appendix A), during the following timeframes:
    a. Systemic and/or topical (vaginal) antifungal treatment, including prescription or over-the-counter products, within 28 days prior to enrollment if administered for the treatment of VVC and during the study for all cases
    b. CYP3A4/5 inducers and strong time-dependent CYP3A4/5 inhibitors during the 14 days prior to enrollment and during study treatment
    c. Strong or moderate reversible CYP3A4/5 inhibitors, including azoles and grapefruit juice, during 48 hours prior to enrollment and during study treatment until TOC
    d. Select CYP2C8 substrates during the 48 hours prior to enrollment or during study treatment
    e. Select P-gp substrates during the 48 hours prior to enrollment or during study treatment SCY-078
3. Subject is actively menstruating at the time of the Baseline visit.
4. Subject has uncontrolled diabetes mellitus.
5. Subject has a vaginal sample with pH >4.5.
6. Subject has a history of or an active cervical/vaginal cancer.

Study Drugs: SCY-078 (150-mg tablets), SCY-078 matching placebo tablets, fluconazole (150-mg capsules) and fluconazole matching placebo capsules.

SCY 078 citrate drug product for oral administration will be supplied as a tablet containing 150 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. Fluconazole study drug will be sourced commercially and will be modified (encapsulated) for the purpose of blinding. Fluconazole will be provided as a capsule containing 150 mg of active ingredient.

The randomized study drugs, SCY-078 (150-mg tablets), SCY-078 matching placebo tablets, fluconazole (150-mg capsules) and fluconazole matching placebo capsules, will be provided by the sponsor.

Study Treatment Groups: Randomized subjects will receive active treatment as detailed below. For all treatment groups, study drug must be administered 30 minutes before or 2 hours after any meal and must be taken with approximately 8 oz./240 mL of water.

<u>Treatment Group 1 (oral SCY-078 750 mg once daily [QD] on Day 1 only):</u>
Subjects randomized to Treatment Group 1 will receive oral SCY-078 750 mg QD on Day 1 only (total daily dose of 750 mg). On randomization day (Baseline [Day 1]), subjects will take 5 tablets of SCY-078 150 mg in the morning.

<u>Treatment Group 2 (oral SCY-078 300 mg twice daily [BID] on Day 1 only):</u>
Subjects randomized to Treatment Group 2 will receive oral SCY-078 300 mg BID on Day 1 only (total daily dose of 600 mg). On randomization day (Baseline [Day 1]), subjects will take 2 tablets of SCY-078 150 mg in the morning and 2 tablets of SCY 078 150 mg in the evening, approximately 12 hours apart.

Treatment Group 3 (oral SCY-078 450 mg BID on Day 1 only):
Subjects randomized to Treatment Group 3 will receive oral SCY-078 450 mg BID on Day 1 only (total daily dose of 900 mg). On randomization day (Baseline [Day 1]), subjects will take 3 tablets of SCY-078 150 mg in the morning and 3 tablets of SCY-078 150 mg in the evening, approximately 12 hours apart.

Treatment Group 4 (oral SCY-078 150 mg BID on Days 1 to 3):
Subjects randomized to Treatment Group 4 will receive oral SCY-078 150 mg BID on Day 1 through Day 3 (total daily dose of 300 mg). On randomization day (Baseline [Day 1]), subjects will take 1 tablet of SCY-078 150 mg in the morning and 1 tablet of SCY-078 150 mg in the evening, approximately 12 hours apart. Over the next 2 consecutive days (Day 2 and Day 3), subjects will take their dose in the morning upon arising and in the evening, approximately 12 hours apart.

Treatment Group 5 (oral SCY-078 300 mg BID on Days 1-3):
Subjects randomized to Treatment Group 5 will receive oral SCY-078 300 mg BID on Days 1 3 (total daily dose of 600 mg). On randomization day (Baseline [Day 1]), subjects will take 2 tablets of SCY-078 150 mg in the morning and 2 tablets of SCY-078 150 mg in the evening, approximately 12 hours apart. Over the next 2 consecutive days (Day 2 and Day 3), subjects will take their dose in the morning upon arising and in the evening, approximately 12 hours apart.

Treatment Group 6 (oral fluconazole 150 mg QD on Day 1 only):
Subjects randomized to Treatment Group 6 will receive oral fluconazole 150 mg QD on Day 1 only (total daily dose of 150 mg). On randomization day (Baseline [Day 1]), subjects will take 1 capsule of fluconazole 150 mg in the morning.

Study Blinding, Randomization: This is a randomized, double-blind, double-dummy study. All site and sponsor personnel will be blinded to treatment assignment, except for a member of the sponsor personnel or a sponsor representative who will be involved in safety activities.

Approximately 180 eligible subjects will be enrolled and randomized in equal allocation to one of the 6 study treatment groups (5 experimental groups and 1 active comparator group). For the purpose of maintaining treatment blinding, all randomized subjects will receive matching SCY-078 placebo tablets and/or matching fluconazole placebo capsules as needed based on treatment assignment, in a double-dummy fashion.

All randomization of subjects will be managed electronically through an interactive voice response system (IWRS). There will be no stratification for this study.

Study Evaluations:

Pharmacokinetic Evaluations:
Blood samples to measure SCY-078 and possible metabolite plasma concentrations will be drawn on Day 3 and Day 10 from the PK Subset, which will consist of 10 subjects per treatment group (total of 60 subjects). On Day 3, samples will be collected at pre-dose (immediately before dosing) and at 2-6 hours' post-dose of either the morning or evening study drug dose. On Day 10, a single PK sample will be collected. For the PK Subset, the TOC visit must occur as close to Day 10 as possible. This sample may be collected at any time of the day. Blood will be collected from all six treatment groups to keep the treatment blinding but only samples from subjects assigned to SCY-078 will be analyzed for PK.

Efficacy Evaluations:
The primary efficacy endpoint of the study is the percentage of subjects with clinical cure (complete resolution of signs and symptoms) at the TOC visit. Secondary efficacy endpoints

include mycological eradication (negative fungal culture) at the TOC visit, a composite endpoint of both clinical cure and mycological eradication at the TOC and FU visits, continued clinical response (continued absence of signs and symptoms) at the FU visit and the time to resolution of signs and symptoms after initiation of study drug. The percentage of subjects with a negative KOH test at the TOC visit, the percentage of subjects who are free of signs and symptoms at the FU visit, the percentage of subjects by *Candida* species infection at Baseline, the percentage of isolates susceptible to SCY-078 and fluconazole, the percentage of subjects with clinical cure (complete resolution of signs and symptoms) at TOC by *Candida* species, and the percentage of subjects with mycological eradication (negative fungal culture) at TOC by *Candida* species will be evaluated as exploratory efficacy endpoints.

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

Clinical Outcomes

- Clinical cure: Complete resolution of signs and symptoms of vulvovaginal infection without need for further antifungal treatment. Specifically, for complete resolution, any sign or symptom should be absent (score = 0) by the TOC visit.
- Clinical failure: No response to therapy or incomplete resolution of signs and symptoms or need for additional vulvovaginal or systemic antifungal therapy. If the subject receives or self-administers topical drug therapy for the treatment of vulvovaginal irritation/pruritus such as topical analgesic or corticosteroid after completing treatment with the study drug and before the TOC visit, the subject is considered a clinical failure.
- Continued Clinical Response: continued absence of signs and symptoms of vulvovaginal infection in subjects who achieved clinical cure at the TOC visit.
- Free of Signs and Symptoms: absence of signs and symptoms of vulvovaginal infection at the FU visit.

Mycological Outcomes

- Mycological eradication: A subject with negative culture (no growth) for *Candida* species.
- Mycological persistence: A subject with a positive culture for *Candida* species.

Safety Evaluations:
Safety will be evaluated throughout the study, including the following parameters: AEs, physical examination, vital signs, safety laboratory tests and treatment discontinuations.

Statistical Analyses:

All statistical processing will be performed using SAS® version 9.3 or later, unless otherwise stated. All statistical tests will be two-sided and interpreted at a 5% significance level. The study is not powered for formal statistical comparisons.

Descriptive statistics (i.e., mean, standard deviation, median, minimum, maximum, etc.) will be provided for all continuous variables; frequencies and percentages will be tabulated for incidence and categorical variables. For parameters measured over time, observed values and changes from baseline will be described for each time point.

All analyses will be presented by treatment group. Unless otherwise stated, data will be analyzed as is with no imputation. No adjustment for multiplicity will be employed.

A Statistical Analysis Plan (SAP) describing all statistical analyses in detail will be provided as a separate document. The SAP will be finalized prior to unblinding of the study treatments.

Sample Size Determination
This is an exploratory study and no formal sample size calculation was performed. Approximately 180 subjects will be enrolled and randomized in an equal allocation (at a 1:1:1:1:1:1 ratio) to the six study treatment groups. Thirty subjects per group are estimated to be adequate to perform an initial assessment of the safety and tolerability as well as the potential efficacy of SCY-078 in subjects with AVVC.

Analysis Populations
Intent-to-Treat (ITT) Population: All randomized subjects.

Modified Intent-to-Treat (mITT) Population: All randomized subjects who have a positive KOH test and a confirmed positive mycological culture for yeast at Baseline.

Per-Protocol (PP) Population: All mITT subjects who have completed the study drug treatment, who have a TOC evaluation AND who have no major protocol deviations.

PK Population: All randomized subjects who received study drug and provided at least one PK sample.

Safety Population: All randomized subjects who received at least one dose of study drug and who have at least one post-Baseline evaluation.

Pharmacokinetic Analyses
PK parameters will be estimated using Population PK (Pop PK) analysis in NONMEM as detailed in the SAP. The PK analyses will be done using the PK Population.

An evaluation of exposure for each dosing regimen relative to clinical cure will be performed.

The concentration versus time data from the PK samples collected in this study will be analyzed using a Pop PK model to predict AUC and C_{max} (as appropriate). A Pop PK modeling strategy is required because the sampling time points will not support a standalone PK analysis, and hence, the data from this study will be pooled with data from other oral studies to predict AUC and C_{max} on Day 1 of treatment. A stand-alone Population PK report will prepared to describe the analysis performed on the PK samples collected from this study.

Further analysis of possible metabolites may be performed.

Efficacy Analyses
The efficacy analyses will be conducted using the mITT (primary analysis population), ITT and PP populations. The efficacy parameters will be evaluated comparing each SCY-078 treatment group (and all treatment groups combined) versus the active comparator (fluconazole) group.

The primary endpoint (clinical cure at TOC) will be analyzed using a Cochran-Mantel-Haenszel row mean scores test. Pairwise treatment comparisons of SCY-078 vs. fluconazole will be performed using a Fisher's Exact test; p-values and 95% confidence intervals will be presented. Subjects whose results are missing at Day 10 (TOC) will be imputed as failures in the analysis. A sensitivity analysis will be performed where subjects with missing values will be removed from the analysis.

For continuous efficacy endpoints, the Student's t-test will be used for pairwise treatment comparisons of SCY-078 vs. fluconazole; p-values and 95% confidence intervals will be presented for the differences between treatment groups. For categorical endpoints, Fisher's Exact test will be performed, and p-values and 95% confidence intervals will be presented. The time to resolution of signs and symptoms after initiation of study drug will be analyzed using Kaplan-Meier methods.

Safety Analyses
Safety analyses will be conducted using the safety population.

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

Safety laboratory evaluations and vital signs will be summarized as observed values and as changes from baseline. In addition, shifts (with respect to the reference range) from baseline will be presented by treatment group for selected laboratory tests.

6.0 Schematic of Study Design

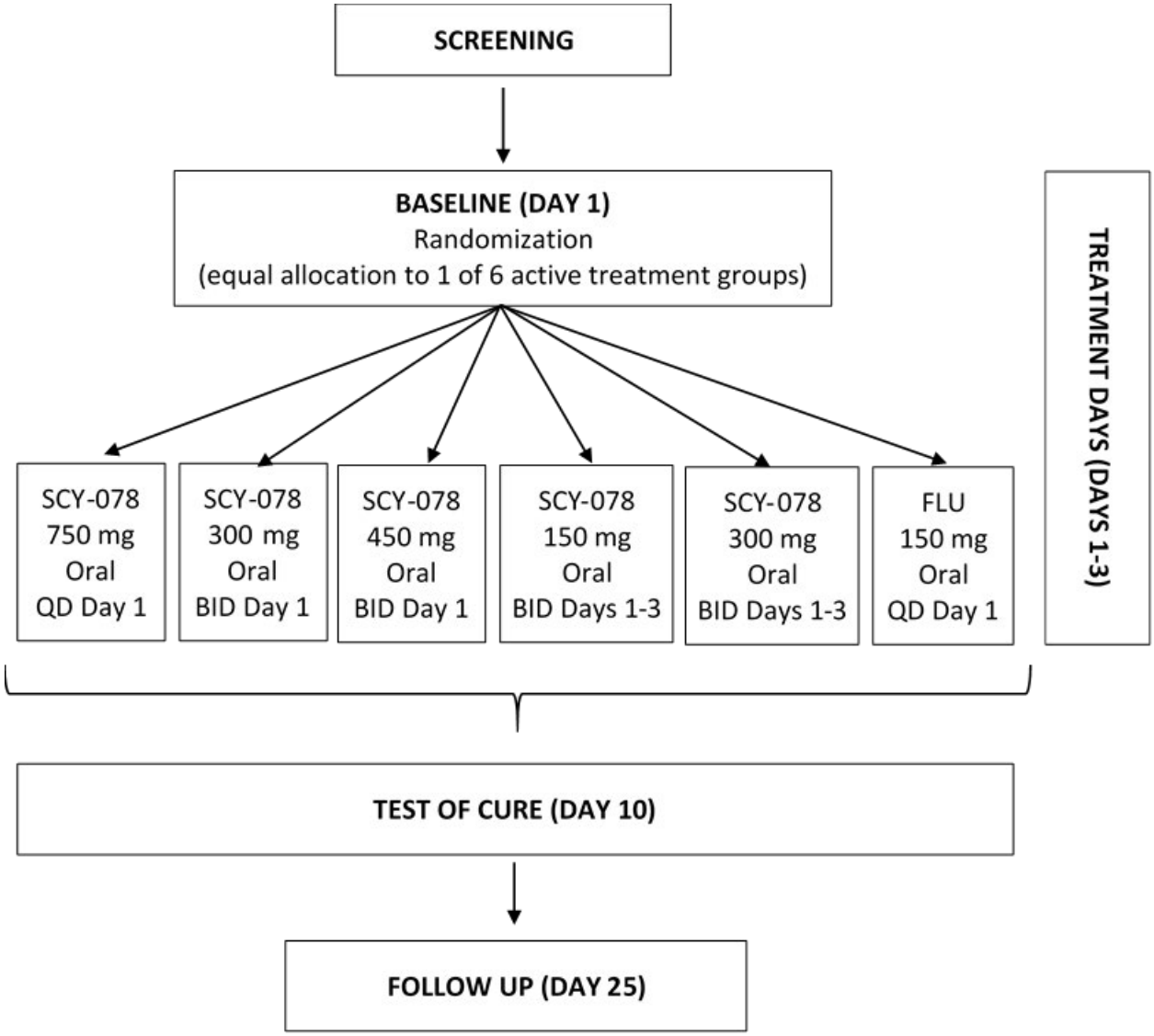

Figure 1 Schematic of Study Design

7.0 Background Information and Scientific Rationale

7.1 Background Information

Vulvovaginal Candidiasis

Vulvovaginal candidiasis (VVC) is a common fungal infection caused by *Candida* spp and is a significant morbidity condition in women from all social classes.

Information on the incidence of VVC is incomplete, since the disease is not a reportable entity and data collection is hampered by inaccuracies of diagnosis and the use of non-representative study populations.[1] VVC affects 70%–75% of women at least once during their lives, most frequently young women of childbearing age. Approximately 40%–50% of women will experience a recurrence[2] and 5% to 8% of adult women have a recurrent vulvovaginal candidiasis.[3] The reported incidence goes from 15% to 30%.[4,5]

Current treatments for VVC include topical antifungals and the use of prescription oral antifungals such a single doses of fluconazole. In two vaginal candidiasis studies conducted with fluconazole, the therapeutic cure rate, defined as the resolution of signs and symptoms of vaginal candidiasis along with negative KOH examination and negative culture for *Candida,* was achieved by 55% of subjects receiving single doses of fluconazole 150 mg. The therapeutic cure rate is reduced to 40% in subjects with a history of recurrent vaginitis.[6,8] Although a single dose of fluconazole is able to provide an acceptable therapeutic outcome for more than half of the treated individuals, the emergence of fluconazole resistance among *C. albicans* isolates and the frequency of cases caused by *C. glabrata,* a strain naturally less susceptible to fluconazole, signals the need for new therapeutic approaches.

Additionally, recurrence of VVC after fluconazole therapy is not uncommon and these exacerbations often involve the same microorganism identified in the initial episode, suggesting that a small number of *C. albicans* remain as a reservoir in the vagina after completion of azole therapy, becoming the source of subsequent exacerbations. This may be explained by the fact that azoles are fungistatic, which means that they slow the growth of, but do not kill, the fungus and azoles are not active against certain species of *Candida* that cause VVC.

New curative approaches are needed, particularly involving agents with fungicidal activity (i.e., that are able to kill the fungus) and activity against fluconazole-resistant strains, so that the causative yeasts can be eradicated. A new therapeutic approach with these characteristics would be expected to result in improved short-term and potentially long-term outcomes for this condition.

This study aims to identify the efficacious dose of SCY-078, as a new class of antifungal agent with fungicidal activity against *Candida* spp. in the treatment of patients with VVC.

The glucan synthesis inhibitor SCY-078

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 synthesis inhibitor (GSI) that inhibits the synthesis of the fungal cell wall polymer β-

(1,3)-D-glucan. Time-kill studies have demonstrated that SCY-078 has *in vitro* fungicidal activity against *Candida* spp. isolates similar to that observed with the echinocandins.

SCY-078 is being developed as the first oral and intravenous (IV) GSI 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.

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)[7] and European Committee on Antimicrobial Susceptibility Testing 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.

Activity against *Candida* spp.

SCY-078 has been evaluated against >1200 *Candida* isolates, including all clinically relevant species, more than 300 *C. glabrata* isolates and 16 *C. auris* isolates. These *in vitro* studies have demonstrated the broad spectrum of anti-*Candida* activity of SCY-078. Additionally, SCY-078 demonstrated *in vitro* activity against pre-formed biofilms, which is a relevant feature when addressing catheter-related *Candida* infections. Studies conducted with azole- and echinocandin-resistant strains have shown that SCY-078 retains activity (i.e., no significant change in minimum inhibitory concentration when compared to wild type) against >90% of azole-resistant strains and >70% of *Candida* strains with *FKS* mutations commonly associated with echinocandin resistance. Interestingly, although 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*). 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. These results suggest that SCY-078 inhibits glucan synthase in a manner different from that of echinocandins.

The *in vitro* studies also included several multidrug-resistant isolates. Consistent with the data described above, SCY-078 was active against >70% of these isolates. SCY-078 has also demonstrated a potent activity against life-threatening and multi-drug-resistant *C. auris* strains

over 16 different *C. auris* isolates, at concentrations indicative of potential clinically relevant effect.[7] *C. auris* has been recently highlighted as a clinical alert by the CDC because of the global emergence of this fungal infection with limited therapeutic options and high mortality.

Activity against *Aspergillus* spp.

The *in vitro* activity of SCY-078 has been evaluated against >150 clinical *Aspergillus* isolates, including most clinically relevant species and azole-resistant strains. The results demonstrated potent activity of SCY-078 against all of the strains tested.

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 concentration-time curve (AUC) in plasma necessary to achieve target efficacy in these models was estimated to be 15.4 ± 2.2 μM•hr.

Nonclinical experience

Toxicology studies in rats and dogs have been conducted with SCY-078 following oral administration for up to 90 days. The results from the non-clinical safety program are supportive of 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 is prohibited.

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. Following three to ten days of IV echinocandin therapy, 21 patients received either SCY-078 or fluconazole. SCY-078 was well tolerated, 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 acute vulvovaginal candidiasis (AVVC) 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 AVVC, 96 patients with an acute, moderate to severe, symptomatic episode of vulvovaginal candidiasis 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-glycoprotein [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 antifungal 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).

7.2 Rationale for the Study

This study is being performed to evaluate the efficacy and safety of different dose levels and dosing regimens of SCY-078 as compared to fluconazole in adult female patients 18 years and older with moderate to severe AVVC.

Rationale for Study Indication and Population

Considering the properties of SCY-078 as a potent antifungal compound, with fungicidal activity against *Candida* spp., it will represent an important non-azole alternative treatment for subjects suffering from AVVC.

Subjects with moderate to severe AVVC are intended for this study to facilitate the identification of a clinically meaningful effect of SCY-078 with a limited sample size.

Rationale for Selected Dose Levels and Dosing Regimens

The SCY-078 dose levels and dosing regimens selected for this study (750 mg QD for 1 day, 300 mg twice daily [BID] for 1 day [total daily dose of 600 mg], 450 mg BID for 1 day [total daily

dose of 900 mg], 150 mg BID for 3 days [total daily dose of 300 mg] or 300 mg BID for 3 days [total daily dose of 600 mg]) are in the range of doses that have been well tolerated in Phase 1 investigations. Since the estimated effective exposure of SCY-078 for vulvovaginal candidiasis has not been determined, this study will contribute to a better understanding of the exposures that may be associated with clinical efficacy for this indication to guide further investigations.

The dose selected for the active comparator of this study (fluconazole) is one single oral dose of 150 mg, which is the recommended and approved dose for this indication.

Rationale for Study Endpoints

The primary endpoint for the study is clinical cure (complete resolution of signs and symptoms) of the acute symptomatic episode at the test-of-cure (TOC) visit on Day 10 (±2), which is in line with current regulatory guidance for this condition.[9] The secondary efficacy endpoints will include mycological eradication (negative fungal culture) at TOC, a composite endpoint of both clinical cure and mycological eradication at the TOC and FU visits, continued clinical response (continued absence of signs and symptoms) at the Follow-up (FU) visit on Day 25 (+4), and time to resolution of signs and symptoms, which are also in line with current guidelines. The safety and tolerability of SCY-078 will also be evaluated as secondary objectives. Other objectives of the study will be to explore the efficacy of SCY-078 based on KOH testing at the TOC visit and based on additional clinical outcomes (clinical response regardless of clinical outcome at TOC) at the FU visit, to explore the prevalence of different *Candida* species, to explore the *in vitro* activity of SCY-078 against baseline *Candida* spp. isolates, to explore clinical and mycological outcomes by *Candida* species, and to evaluate the PK of SCY-078.

Rationale for Study Design

This trial is being conducted as a double-blind, double-dummy study. This design is considered an appropriate design for this indication and phase of investigation, and will use matching SCY-078 and fluconazole placebo to accommodate the differences in the dosing regimens and formulations of SCY-078 and the comparator (fluconazole).

The data generated from this study will provide an initial characterization of the safety and tolerability of SCY-078 in subjects with AVVC, and will provide an initial indication of the most effective dosing regimen with efficacy of SCY-078 in this condition. Results from this study will guide subsequent phases of development for this indication.

8.0 Study Objectives

8.1 Primary Objectives

- To identify the recommended dose of oral SCY-078 in subjects with moderate to severe AVVC by comparing the efficacy of different dose levels and dosing regimens of oral SCY-078

8.2 Secondary Objectives

- To evaluate the efficacy of oral SCY-078 in subjects with AVVC based on mycological and clinical outcomes
- To evaluate the safety and tolerability of different dose levels and dosing regimens of oral SCY-078 in subjects with AVVC

8.3 Exploratory Objectives

- To explore the efficacy of SCY-078 in subjects with AVVC based on potassium hydroxide (KOH) testing at the TOC visit
- To explore the efficacy of SCY-078 in subjects with AVVC based on additional clinical outcomes
- To explore the prevalence of *Candida* species among subjects with AVVC
- To explore the *in vitro* activity of SCY-078 against baseline *Candida* spp. isolates
- To explore clinical and mycological outcomes by *Candida* species
- To evaluate the PK of SCY-078 after oral administration of different dose levels and dosing regimens of SCY-078 in subjects with AVVC

9.0 Study Endpoints

9.1 Primary Endpoints

- Efficacy as measured by the percentage of subjects with clinical cure (complete resolution of signs and symptoms) at the TOC visit

9.2 Secondary Endpoints

Efficacy as measured by:

- The percentage of subjects with mycological eradication (negative fungal culture) at the TOC visit

- The percentage of subjects with both clinical cure and mycological eradication at the TOC and FU visits.
- The percentage of subjects with continued clinical response (continued absence of signs and symptoms) at the Follow-up (FU) visit.
- The time to resolution of signs and symptoms after initiation of study drug

Safety and tolerability as measured by:

- AEs, treatment discontinuations, vital signs, physical examination and safety laboratory tests

9.3 Exploratory Endpoints

- Percentage of subjects with a negative KOH test at the TOC visit
- Percentage of subjects who are free of signs and symptoms at the FU visit
- Percentage of subjects by *Candida* species infection at Baseline
- Percentage of isolates susceptible to SCY-078 and fluconazole
- Percentage of subjects with clinical cure (complete resolution of signs and symptoms) at TOC by *Candida* species
- Percentage of subjects with mycological eradication (negative fungal culture) at TOC by *Candida* species
- Determination of the PK parameters (C_{max} and AUC) for each dosing regimen and evaluation of the dose/exposure relationship relative to clinical outcome

10.0 Study Design

10.1 Overall Description of the Study

This is a multicenter, randomized, double-blind, double-dummy, active-controlled, dose-finding study to compare the efficacy, safety and tolerability of oral SCY-078 compared to oral fluconazole in adult female subjects 18 years and older with moderate to severe AVVC. Approximately 180 eligible subjects (30 subjects per treatment group) will be enrolled and randomized into the study.

The primary objective of this study is to identify the recommended dose of oral SCY-078 in subjects with moderate to severe AVVC by comparing the efficacy of different dose levels and dosing regimens of SCY-078.

The study will consist of a Screening visit, a Baseline visit on Day 1, a study visit on Day 3 (which will consist of an on-site visit for PK sampling for a subset of subjects and a phone contact for all other subjects), a TOC visit (which will include PK sampling for the PK Subset of subjects) on Day 10 (±2) and a FU visit on Day 25 (+4). The Screening and Baseline visits may be combined. Efficacy, safety, tolerability and PK assessments will be conducted for the study.

Efficacy will be determined primarily by the percentage of subjects with clinical cure (complete resolution of signs and symptoms) at the TOC visit. Secondary efficacy endpoints will include mycological eradication (negative fungal culture) at the TOC visit, a composite endpoint of both clinical cure and mycological eradication at the TOC and FU visits, continued clinical response (continued absence of signs and symptoms) at the FU visit, and the time to resolution of signs and symptoms after initiation of study drug. Other efficacy endpoints will also be explored. Safety and tolerability will be evaluated throughout the study, including the following parameters: physical exam, vital signs, AEs, treatment discontinuations and safety laboratory tests. A subset of approximately 60 subjects will also undergo blood sampling for PK analyses of SCY-078 in plasma.

A summary description of the study visits and assessments is provided below. A schematic of the study design is available in Section 6.0. Detailed descriptions of study treatments and procedures are provided in Section 12.0 and Section 14.0, respectively**.**

10.1.1 Study Visits

Screening (Day -1)

Consenting subjects who are experiencing vulvovaginal symptoms at Screening will be evaluated by the investigator, who will obtain a vaginal sample for local KOH testing and for fungal culture and species identification by the central laboratory. Susceptibility testing will be done at the central laboratory for all positive cultures for *Candida* spp. Additional vaginal samples will be collected, if clinically indicated, to be examined for the presence of other pathogens (e.g., causative agents for bacterial vaginosis, *Trichomonas*, *Herpes* virus, *N. gonorrhea*, *Chlamydia*, human papillomavirus or other mixed infections) by a qualified laboratory (central or local laboratory) and for the determination of vaginal pH by the investigator. The investigators and the subjects will rate the signs (edema, erythema and excoriation) and symptoms (itching, burning and irritation) of infection, respectively, on a standardized vulvovaginal signs and symptoms scale (the Vulvovaginal Signs and Symptoms [VSS] Scale) (see Appendix B). Safety procedures, including an abbreviated physical exam, vital signs, laboratory tests and a pregnancy test will also be performed.

To be eligible for inclusion, subjects must have a minimum composite score of vulvovaginal signs and symptoms ≥7 with at least 2 signs or symptoms having a score of 2 (moderate) or greater in the VSS Scale, a positive KOH test and a normal vaginal pH (≤4.5).

Baseline (Day 1)

At the Baseline visit (which may be combined with the Screening visit), eligible subjects will be randomized in equal allocation (at a 1:1:1:1:1:1 ratio) to one of the following 6 active treatment groups (5 experimental groups and 1 active comparator group):

- Treatment Group 1: oral SCY-078 750 mg QD on Day 1 only
- Treatment Group 2: oral SCY-078 300 mg BID on Day 1 only
- Treatment Group 3: oral SCY-078 450 mg BID on Day 1 only
- Treatment Group 4: oral SCY-078 150 mg BID on Days 1 to 3
- Treatment Group 5: oral SCY-078 300 mg BID on Days 1 to 3
- Treatment Group 6: oral fluconazole 150 mg QD on Day 1 only

For the purpose of maintaining treatment blinding, all randomized subjects will receive matching SCY-078 placebo tablets and/or matching fluconazole placebo capsules as needed based on treatment assignment, in a double-dummy fashion. Study drug treatment will be dispensed on Day 1 and will be self-administered by the subjects from Day 1 (Baseline) through Day 3. Subjects will also be given subject diaries to rate their symptoms of infection on the VSS scale and to record dosing details, AEs and concomitant medication use daily from Day 1 through the TOC visit (Day 10).

Day 3

On Day 3, a PK Subset consisting of 10 subjects per treatment group (total of 60 subjects) will visit the site to have PK samples drawn pre-dose (immediately before dosing) and at 2-6 hours' post-dose of either the morning or evening dose. Day 3 will be an on-site visit for PK subjects and a phone contact visit (with a window of +3 days) for non-PK subjects. All subjects (both PK and non-PK subjects) will continue to take their assigned study treatment and rate their symptoms of infection on their subject diaries. Treatment compliance will be reviewed either on site or by phone for all subjects. Study drug may be collected from PK subjects who have completed study drug dosing at the time of this visit.

TOC (Day 10)

Vaginal samples will be obtained for local KOH testing and for fungal culture by the central laboratory. In addition, susceptibility testing will be done at the central laboratory for all positive cultures for *Candida* spp. The investigators and the subjects will rate the signs and symptoms of infection, respectively, on the VSS Scale. An abbreviated physical exam, vital sign measurements and safety laboratory tests will also be performed. Additionally, a single PK sample will be obtained at any convenient time of the day from the PK Subset only. For the PK Subset, the TOC

visit must occur as close to Day 10 as possible. All subjects will return their subject diaries. Compliance with study drug dosing will be evaluated and study drug will be collected for all subjects who did not return their study drug on Day 3.

FU (Day 25)
Vaginal samples will be obtained for local KOH testing and for fungal culture by the central laboratory. In addition, susceptibility testing will be done at the central laboratory for all positive cultures for *Candida* spp. The investigators and the subjects will rate the signs and symptoms of infection on the VSS Scale to evaluate clinical outcome.

All Visits
AEs and prior/concomitant medications will be assessed and documented at all visits.

10.1.2 Study Assessments

The study will include efficacy, safety and PK assessments.

Efficacy Assessments
Treatment outcome will be assessed primarily based on clinical cure (complete resolution of signs and symptoms) at the TOC (Day 10) visit. Secondary efficacy endpoints will include mycological eradication (negative fungal culture) at the TOC visit, a composite endpoint of both clinical cure and mycological eradication at the TOC and FU visits, continued clinical response (continued absence of signs and symptoms) at the FU visit and time to resolution of signs and symptoms after initiation of study drug. Additionally, the percentage of subjects with a negative KOH test at the TOC visit, the percentage of subjects who are free of signs and symptoms at the FU visit, the percentage of subjects by *Candida* species infection at Baseline, the percentage of isolates susceptible to SCY-078 and fluconazole will be explored, the percentage of subjects with clinical cure (complete resolution of signs and symptoms) at TOC by *Candida* species and the percentage of subjects with mycological eradication (negative fungal culture) at TOC by *Candida* species will be evaluated as exploratory efficacy endpoints.

Clinical Evaluation
The signs (edema, erythema and excoriation or fissures) and symptoms (itching, burning and irritation) of infection will be assessed by the investigator and the subject, respectively, on the VSS Scale [provided in Appendix B]). The VSS Scale is a standardized, predefined scale where each sign and symptom will be given a numerical rating based on severity (absent = 0; mild = 1; moderate = 2; severe = 3) to calculate a total composite score.

Mycological Testing

Mycological tests will include direct microscopic examination with 10% KOH and fungal cultures. KOH will be performed locally at Screening for the determination of subject eligibility and at the TOC and FU visits for the exploratory assessment of treatment outcome. Fungal cultures will be performed centrally at Screening for species identification and susceptibility testing and at the TOC and FU visits for the assessment of treatment outcome and susceptibility testing for subjects with positive cultures.

Pharmacokinetic Assessments

Blood samples will be drawn on Day 3 and Day 10 (±2) from the PK Subset (10 subjects per treatment group) for the determination of SCY-078 and possible plasma metabolite concentrations. For the PK Subset, the TOC visit must occur as close to Day 10 as possible. Blood will be collected from all six treatment groups to keep treatment blinding but only samples from subjects assigned to SCY-078 will be analyzed for PK.

Safety Assessments

Safety procedures will include an abbreviated physical exam, vital signs, pregnancy test, safety laboratory tests, AEs and review of concomitant medication use.

10.2 Blinding, Randomization and Stratification

This is a randomized, double-blind, double-dummy study. All site and sponsor personnel will be blinded to treatment assignment, except for a member of the sponsor personnel or a sponsor representative who will be involved in safety activities.

Approximately 180 eligible subjects will be enrolled and randomized in equal allocation (at a 1:1:1:1:1:1 ratio) to one of the 6 study treatment groups (5 experimental groups and 1 active comparator group). For the purpose of maintaining treatment blinding, all randomized subjects will receive matching SCY-078 placebo tablets and/or matching fluconazole placebo capsules as needed based on treatment assignment, in a double-dummy fashion.

All randomization of subjects will be managed electronically through an interactive voice response system (IWRS).

There will be no stratification for this study.

10.3 Study Duration

Each subject is expected to complete the study within approximately 30 days.

10.4 Number of Centers

Approximately 20 study centers are expected to participate in subject enrollment and treatment.

11.0 Study Population

The study population will include adult female subjects 18 years and older, with moderate to severe AVVC.

11.1 Inclusion Criteria

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

1. Subject is a female subject 18 years and older and is in good general health based on medical history, physical examination, vital sign measurements and safety laboratory tests performed at the Screening visit and/or prior to administration of the initial dose of study drug.
2. Subject has a diagnosis of symptomatic AVVC that meets the following criteria:
    a. Moderate to severe disease, defined as a minimum composite vulvovaginal signs and symptoms score of ≥7, with at least 2 signs or symptoms having a score of 2 (moderate) or greater in the VSS Scale at Baseline
    b. Positive microscopic examination with 10% KOH in a vaginal sample collected at Screening revealing yeast forms (hyphae/pseudohyphae) or budding yeasts
    c. Normal vaginal pH (≤4.5)
3. Subject is not pregnant and is highly unlikely to become pregnant since 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 (e.g. anorexia nervosa).
    b. Subject is a female subject who is of reproductive potential and agrees to remain abstinent or use (or have 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.

Hormonal contraception, including but not limited to oral, injectable or implantable methods, are not acceptable as a single method of contraception because the effect of SCY-078 on the efficacy of oral contraceptive pills has not yet been established.

Subjects must refrain from using any vaginal contraceptives as these may have an impact on the signs and symptoms of AVVC.

Note: Women of childbearing potential must have a negative urine pregnancy test prior to enrollment (performed by the site's local laboratory).

4. Subject is able to understand and sign a written informed consent form (ICF), which must be obtained prior to treatment and any study-related procedures.
5. Subject 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 Health Information Portability and Accountability Act Authorization form).
6. Subject is able to understand and follow all study-related procedures including study drug administration.

11.2 Exclusion Criteria

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

1. Subject has any vaginal condition other than AVVC that may interfere with the diagnosis or evaluation of response to therapy, such as suspected or confirmed concurrent causes of vulvovaginitis and/or cervicitis including bacterial vaginosis, *Trichomonas*, active *Herpes* virus, *N. gonorrhea*, *Chlamydia*, active human papillomavirus or other mixed infections.
2. Subject requires treatment with the prohibited medications (including prescription and over-the-counter medications, supplements, and herbal products) listed in Section 21.0 (Appendix A), during the following timeframes:
    a. Systemic and/or topical (vaginal) antifungal treatment, including prescription or over-the-counter products, within 28 days prior to enrollment if administered for the treatment of VVC and during the study for all cases
    b. CYP3A4/5 inducers and strong time-dependent CYP3A4/5 inhibitors during the 14 days prior to enrollment and during study treatment
    c. Strong or moderate reversible CYP3A4/5 inhibitors, including azoles and grapefruit juice, during 48 hours prior to enrollment and during study treatment until TOC

d. Select CYP2C8 substrates during the 48 hours prior to enrollment or during study treatment

e. Select P-gp substrates during the 48 hours prior to enrollment or during study treatment SCY-078

3. Subject is actively menstruating at the time of the Baseline visit.
4. Subject has uncontrolled diabetes mellitus.
5. Subject has a vaginal sample with pH >4.5.
6. Subject has a history of or an active cervical/vaginal cancer.
7. Subject has a known hypersensitivity to SCY-078, fluconazole or any of the components of the formulation.
8. Subject has a known human immunodeficiency virus infection and/or is receiving chemotherapy or has an illness that, in the judgment of the investigator, is serious enough to induce an immune deficiency.
9. Subject has had any major illness within 30 days before Screening.
10. Subject is pregnant or lactating.
11. 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.
12. Subject has received prior treatment with the study drug in a previous trial.
13. 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.
14. Subject is an employee of SCYNEXIS, Inc., the investigator or the 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.
15. Subject is unlikely to comply with protocol requirements.

11.3 Discontinuation Criteria

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

- Withdrawal of consent;
- Investigator or sponsor decision that withdrawal is in the subject's best interest;
- Occurrence of an AE that, in the opinion of the investigator, warrants discontinuation of the subject from the study drug;

- 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 TOC procedures should be performed for subjects who discontinue from the study before the TOC visit. All FU visit procedures should be done for subjects who discontinue after the TOC visit but before the FU visit.

11.4 Replacement of Dropouts

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

12.0 Study Treatments

Subjects who meet all of the inclusion and none of the exclusion criteria will be enrolled into the study and will be randomized in equal allocation (at a 1:1:1:1:1:1 ratio) to one of the following 6 active treatment groups of the study (5 experimental groups and 1 active comparator group):

- Treatment Group 1: oral SCY-078 750 mg QD on Day 1 only
- Treatment Group 2: oral SCY-078 300 mg BID on Day 1 only
- Treatment Group 3: oral SCY-078 450 mg BID on Day 1 only
- Treatment Group 4: oral SCY-078 150 mg BID on Days 1 to 3
- Treatment Group 5: oral SCY-078 300 mg BID on Days 1 to 3
- Treatment Group 6: oral fluconazole 150 mg on Day 1 only

For the purpose of maintaining treatment blinding, all randomized subjects will receive matching SCY-078 placebo tablets and/or matching fluconazole placebo capsules as needed based on treatment assignment, in a double-dummy fashion. A summary of dose levels, dosing days, total daily dose, tablet strength and tablet quantity for each treatment group is provided in Table 1.

Table 1: Study Treatment Groups (Study SCY-078-204)

Treatment Group	Dose Level	Dosing Day			Total Daily Dose	Strength/Number of Tablets/Capsules per Dose
		Day 1	Day 2	Day 3		
Group 1	SCY-078 750 mg	QD			SCY-078 750 mg	150-mg tablet/5 tablets
Group 2	SCY-078 300 mg	BID			SCY-078 600 mg	150-mg tablet/2 tablets
Group 3	SCY-078 450 mg	BID			SCY-078 900 mg	150-mg tablet/3 tablets
Group 4	SCY-078 150 mg	BID	BID	BID	SCY-078 300 mg	150-mg tablet/1 tablets
Group 5	SCY-078 300 mg	BID	BID	BID	SCY-078 600 mg	150-mg tablet/2 tablets
Group 6 (comparator)	FLU 150 mg	QD			FLU 150 mg	150-mg capsule/ 1 capsule

Abbreviations: BID = twice daily; FLU = fluconazole; QD = once daily

12.1 Study Treatment Groups

Randomized subjects will receive active treatment as detailed below. For the purpose of maintaining treatment blinding, all randomized subjects will receive matching SCY-078 placebo tablets and/or matching fluconazole placebo capsules as needed based on treatment assignment, in a double-dummy fashion. All study drug will be self-administered by the subjects.

Treatment Group 1 (oral SCY-078 750 mg QD on Day 1 only):
Subjects randomized to Treatment Group 1 will receive oral SCY-078 750 mg QD on Day 1 only (total daily dose of 750 mg). On randomization day (Baseline [Day 1]), subjects will take 5 tablets of SCY-078 150 mg in the morning. Study drug must be administered 30 minutes before or 2 hours after any meal and must be taken with approximately 8 oz./240 mL of water.

Treatment Group 2 (oral SCY-078 300 mg BID on Day 1 only):
Subjects randomized to Treatment Group 2 will receive oral SCY-078 300 mg BID on Day 1 only (total daily dose of 600 mg). On randomization day (Baseline [Day 1]), subjects will take 2 tablets of SCY-078 150 mg in the morning and 2 tablets of SCY-078 150 mg in the evening, approximately 12 hours apart. Study drug must be administered 30 minutes before or 2 hours after any meal and must be taken with approximately 8 oz./240 mL of water.

Treatment Group 3 (oral SCY-078 450 mg BID on Day 1 only):
Subjects randomized to Treatment Group 3 will receive oral SCY-078 450 mg BID on Day 1 only (total daily dose of 900 mg). On randomization day (Baseline [Day 1]), subjects will take 3 tablets of SCY-078 150 mg in the morning and 3 tablets of SCY-078 150 mg in the evening, approximately 12 hours apart. Study drug must be administered 30 minutes before or 2 hours after any meal and must be taken with approximately 8 oz./240 mL of water.

Treatment Group 4 (oral SCY-078 150 mg BID on Days 1 to 3):
Subjects randomized to Treatment Group 4 will receive oral SCY-078 150 mg BID on Day 1 through Day 3 (total daily dose of 300 mg). On randomization day (Baseline [Day 1]), subjects will take 1 tablet of SCY-078 150 mg in the morning and 1 tablet of SCY-078 150 mg in the evening, approximately 12 hours apart. Over the next 2 consecutive days (Day 2 and Day 3), subjects will take their dose in the morning upon arising and in the evening, approximately 12 hours apart. Study drug must be administered 30 minutes before or 2 hours after any meal and must be taken with approximately 8 oz./240 mL of water.

Treatment Group 5 (oral SCY-078 300 mg BID on Days 1-3):
Subjects randomized to Treatment Group 5 will receive oral SCY-078 300 mg BID on Days 1-3 (total daily dose of 600 mg). On randomization day (Baseline [Day 1]), subjects will take 2 tablets of SCY-078 150 mg in the morning and 2 tablets of SCY-078 150 mg in the evening, approximately 12 hours apart. Over the next 2 consecutive days (Day 2 and Day 3), subjects will

take their dose in the morning upon arising and in the evening, approximately 12 hours apart. Study drug must be administered 30 minutes before or 2 hours after any meal and must be taken with approximately 8 oz./240 mL of water.

Treatment Group 6 (oral fluconazole 150 mg QD on Day 1 only):
Subjects randomized to Treatment Group 6 will receive oral fluconazole 150 mg QD on Day 1 only (total daily dose of 150 mg). On randomization day (Baseline [Day 1]), subjects will take 1 capsule of fluconazole 150 mg in the morning. Study drug must be administered 30 minutes before or 2 hours after any meal and must be taken with approximately 8 oz./240 mL of water.

12.2 Dietary Requirements

For all treatment groups, oral study drug must be administered 30 minutes before or 2 hours after any meal and must be taken with approximately 8 oz./240 mL of water.

Nutraceuticals and foods that are known CYP3A inhibitors, such as grapefruit juice, blood oranges and mulberry juice should not be consumed until the last PK sample is collected (TOC) (see Section 21.0 [Appendix A]).

12.3 Study Drugs

The randomized study drugs, SCY-078 (150-mg tablets), SCY-078 matching placebo tablets, fluconazole (150-mg capsules) and fluconazole matching placebo capsules, will be provided by the Sponsor.

12.3.1 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]

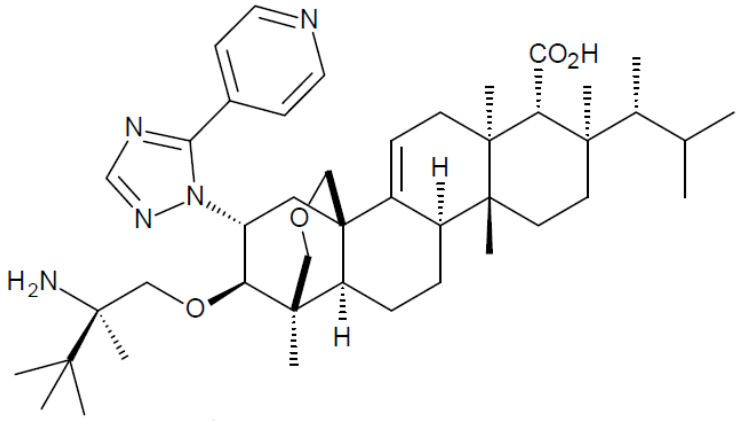

Figure 2 Chemical Structure of SCY-078 Citrate

12.3.2 Formulation, Packaging and Labelling

SCY-078 citrate drug product for oral administration will be supplied as a tablet containing 150 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.

Fluconazole study drug will be sourced commercially and will be modified (encapsulated) for the purpose of blinding. Fluconazole will be provided as a capsule containing 150 mg of active ingredient.

Study drug supplies will be packaged in a treatment kit, a box containing bottles (active drug plus matching placebo), for all three study treatment days (Days 1-3).

Bottles will contain the following active treatment:

- Treatment Group 1: 5 tablets of SCY-078
- Treatment Group 2: 4 tablets of SCY-078
- Treatment Group 3: 6 tablets of SCY-078
- Treatment Group 4: 6 tablets of SCY-078 (2 tablets each for Day 1, Day 2 and Day 3)
- Treatment Group 5: 12 tablets of SCY-078 (4 tablets each for Day1, Day 2 and Day 3)
- Treatment Group 6: 1 capsule of fluconazole

For the purpose of blinding, the number and appearance of dosage units will be the same across all treatment groups, as follows:

- Day 1: 5 tablets for the morning dose + 3 tablets and 1 capsule for the evening dose

- Day 2 and Day 3: 2 tablets for the morning dose + 2 tablets for the evening dose

Labels on the kits and/or bottles containing study medication will include the following information and any other information required by applicable regulations:

- Sponsor Name
- Study Protocol Number
- Place to write the subject number
- Number of tablets/capsules count per bottle or box
- Dosing instructions
- Storage conditions
- Caution Statement: "Caution: New Drug – Limited by Federal (United States) Law to Investigational Use Only"

12.3.3 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.

12.4 Drug Accountability

The investigator or designee will inventory and acknowledge receipt of all shipments of the study drug. An IWRS will be used to dispense study drugs to individual subjects. 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 12.3.3).

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

This is a double-blind, double-dummy study. All site and sponsor personnel will be blinded to treatment assignment, except for a member of the sponsor personnel or a sponsor representative

who will be involved in safety activities. A study site designee (e.g. pharmacist, study nurse/coordinator) will:

- Record the treatment in the appropriate drug accountability log
- 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 and capsules remaining at the TOC (Day 10) visit (or Day 3, if applicable)
- Review subject diary and tablet/capsule count, and record any unused or remaining drug in the drug accountability log and eCRF and note any discrepancies and reason for discrepancies

12.5 Subject Compliance with Study Drug Dosing

Treatment compliance will be reviewed at the Day 3 and TOC (Day 10) visits. PK subjects who have completed study drug dosing at the time of their Day 3 visit may have study drug collected on Day 3. Study drug will be collected at the TOC (Day 10) visit for all other subjects.

Subjects will be instructed to have the assigned treatment kit of study medication (including empty bottles) with them at these visits. Compliance will be assessed based on remaining tablets as compared to what should have been taken and based on the subject diary where the subject will enter the details of study drug dosing (Section 14.13). Details of treatment including any missing dose will be recorded on the eCRF. Sites are encouraged to contact the medical monitor or sponsor for concerns of compliance with the treatment regimen, especially for subjects who miss doses due to problems with tolerability.

13.0 Non-Study Treatments

13.1 Prior and Concomitant Medications

All medications (including prescription and over-the-counter medications, supplements, and herbal products) taken from 28 days before Baseline (Day 1) through the TOC visit 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 the TOC visit through the last study visit (FU). Start and stop dates of concomitant medications taken during antifungal therapy will be recorded on the eCRF. Prior and concomitant medications will be reviewed and recorded at all study visits.

Certain concomitant medications must be administered with caution or close monitoring as described in Appendix A Section 21.0.

13.2 Prohibited Medications

Medications specifically not permitted in the exclusion criteria (Section 11.2) include the following:

- Non-study systemic or topical antifungal therapy
- Topical vaginal corticoids
- Vaginal contraceptives
- Other investigational drug(s)
- Strong CYP3A4/5 inhibitors, select moderate CYP3A4/5 inhibitors, CYP3A4/5 inducers, select CYP2C8 substrates and select P-gp substrates.

See Section 21.0 (Appendix A) for the full list of prohibited medications.

13.3 Medications to be Administered with Caution and Monitored as Appropriate

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

- Moderate CYP3A4/5 inhibitors (except for the select prohibited moderate CYP3A4/5 inhibitors)
- CYP3A4 substrates, including but not limited to sirolimus, tacrolimus and warfarin
- Organic anion-transporting polypeptide 1B3 (OATP1B3) substrates

See Section 21.0 (Appendix A) for the full list of medications to be administered with caution.

13.4 Study Restrictions

There are no additional study restrictions other than those described in Sections 11.2 (Exclusion Criteria), Section 12.2 (Dietary Requirements) and Section 13.2 (Prohibited Medications).

14.0 Study Procedures

The following sections provide a description of the individual study procedures to be performed during the conduct of the study. Detailed schedules of study assessments are provided in the Schedule of Visits and Procedures in Table 2.

14.1 Informed Consent

Every study subject must provide written informed consent at Screening, prior to participating in any Screening evaluations or any other study activities (see Section 19.3).

14.2 Assignment of Subject Number

At Screening, all subjects who have signed an ICF will receive a unique subject identification (ID) number, which will consist of a 4-digit subject ID number that will be composed of a 2-digit site number followed by a 2-digit sequentially assigned subject number starting at 01, at each site. For instance, the first subject from site 01 will have 0101 as her assigned subject number and the subsequent subject from this site will have 0102 as her assigned subject number. The first subject from site 02 will have 0201 as her assigned subject number and the subsequent subject from this site will have 0202 as her assigned subject number. The subject numbers assigned to eligible subjects will be recorded in the eCRF. This number will be unique to each subject and will be used to identify the subject throughout the study. This number is different from the treatment bottle number.

Subjects who are screen failures or who are not eligible for randomization will be recorded as such in the eCRF. For subjects who sign an ICF (i.e., are assigned a subject number) but are NOT assigned a treatment assignment number because they do not meet all of the inclusion/exclusion criteria, the applicable Screening visit pages of the eCRF will be completed. The criteria that were not met for randomization will be documented in the eCRF.

14.3 Inclusion and Exclusion Criteria

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

14.4 Medical History and Demographics

During the Screening visit, a complete medical history for the prior year will be recorded for each subject. The medical history will include previous and current medical diagnoses and major surgical procedures. Subject demographics such as age, sex, race and ethnicity will also be collected.

14.5 Abbreviated Physical Examination

An abbreviated physical examination, including general appearance and an overall examination of body systems, will be conducted at Screening and at the TOC visit.

14.6 Urine Pregnancy Test

A urine pregnancy test will be performed at Screening and at unscheduled visits (if needed) by the local laboratory for all subjects of childbearing potential. The pregnancy test results will be reviewed at Baseline (Day 1) before starting/dispensing study drug.

14.7 Safety Laboratory Tests

Safety laboratory tests will be performed by a qualified central laboratory. Safety laboratory tests will also be performed at the Screening, TOC visit and at unscheduled visits, if needed. If indicated, these may 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 lymphocytes, monocytes, eosinophils and basophils, and absolute counts for neutrophils, lymphocytes, atypical lymphocytes, monocytes, eosinophils and basophils.

Blood Chemistry

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

14.8 Vulvovaginal Samples for Identification of Other Pathogens and Vaginal pH

A vulvovaginal specimen will be obtained and assessed locally at the Screening visit to rule out bacterial vaginosis and *Trichomonas.* Testing for *N. gonorrhea*, *Chlamydia* or *Herpes* virus will also be conducted by a qualified laboratory (local or central laboratory), if clinically indicated. Vaginal samples will be tested for bacterial vaginosis, *Trichomonas, N. gonorrhea*, *Chlamydia* or

Herpes virus at unscheduled visits only if needed. Vulvovaginal specimens will also be obtained at the Screening visit for local vaginal pH determination.

Procedures for collecting and shipping vulvovaginal samples are described in the laboratory manual.

14.9 Vulvovaginal Samples for KOH and Fungal Culture

At Screening, a vulvovaginal specimen will be obtained for direct microscopic examination with 10% KOH. Subjects must have a positive KOH test at Screening to be randomized to one of the study treatment groups. The Screening KOH will be assessed at the site by the investigator or designee. A vaginal sample will also be obtained at Screening for fungal culture and species identification by the central laboratory and for susceptibility testing against SCY-078, fluconazole and additional antifungal agents. Central susceptibility testing will be done as per CLSI M27-A3 guidelines. An additional vulvovaginal specimen will be collected at the TOC and FU visits for local KOH testing and for fungal culture by the central laboratory for treatment outcome assessment. In addition, susceptibility testing will be done at the central laboratory for all positive cultures for *Candida* spp. Vulvovaginal samples may also be taken at unscheduled visits, if needed.

14.10 Rating of Vulvovaginal Signs by the Investigator Using the VSS Scale

The investigator (or qualified designee) will perform vulvovaginal examinations to rate the subject´s signs of infection at the Screening, TOC and FU visits, as well as at unscheduled visits. Investigators will assess the signs of infection using the VSS Scale provided in Section 21.0 [Appendix B]), a standardized, predefined scale. where each sign of the vagina and/or vulva will be given a numerical rating based on severity, as follows:

- Edema: absent = 0; mild = 1; moderate = 2; severe = 3
- Erythema: absent = 0; mild = 1; moderate = 2; severe = 3
- Excoriation or fissures: absent = 0; mild = 1; moderate = 2; severe = 3

Other findings will be recorded using the most relevant medical term in the abbreviated physical examination page of the eCRF.

14.11 Rating of Vulvovaginal Symptoms by the Subject Using the VSS Scale

Subjects will be asked to rate their vulvovaginal symptoms at Screening, from Day 1 through the TOC visit (Day 10), at the FU visit and at any unscheduled visit.

Subjects will rate their symptoms of infection using the VSS Scale (see Appendix B), where each vulvovaginal symptom will be given a numerical rating based on severity, as follows:

- Itching: absent = 0; mild = 1; moderate = 2; severe = 3
- Burning: absent = 0; mild = 1; moderate = 2; severe = 3
- Irritation: absent = 0; mild = 1; moderate = 2; severe = 3

From Day 1 through the TOC visit, subjects will rate their symptoms and record their scores on the VSS Scale included in their subject diaries.

14.12 Randomization

At Baseline (Day 1), subjects who meet all of the inclusion and none of the exclusion criteria will be randomized to one of the six study treatment groups. Subject randomization will be performed using an IWRS, which will assign a unique randomization number for each randomized subject corresponding to a study treatment. Only one randomization number and study drug treatment will be assigned to each eligible subject.

14.13 Study Drug and Subject Diary Dispensing

At Baseline (Day 1), subjects will be dispensed bottles containing study medication (see Section 12.3.2) and a subject diary that they will complete daily from Day 1 through the TOC (Day 10) visit.

14.14 Study Drug Dosing

Study drug doses will be self-administered by the subjects from Baseline (Day 1) through Day 3. Details of study treatment groups and dietary requirements for treatment administration are provided in Section 12.1 and Section 12.2, respectively.

14.15 Subject Diary Completion

Subjects will complete their diaries from Day 1 through the TOC visit. The subject diaries will include the VSS Scale so that subjects can rate their vulvovaginal symptoms. Subjects will record the date of study medication dosing, daily vulvovaginal symptoms, other medical concerns or complaints and concomitant medications used. Subjects will be instructed to return their subject diaries at the TOC visit (Day 10).

After the TOC visit, subjects will not be required to complete a diary but will be instructed to call the site immediately if they experience new or worsening signs/symptoms or medical concerns/complaints. The site will also determine if any signs/symptoms or other medical concerns/complaints recorded on the diary should be reported as AEs. The information from the subject diary will be included as part of the eCRFs.

14.16 Treatment Compliance Evaluation and Study Drug Collection

Treatment compliance will be reviewed by the investigator or designee at the Day 3 and TOC (Day 10) visits. PK subjects who have completed study drug dosing at the time of their Day 3 visit may have study drug collected on Day 3. Study drug will be collected at the TOC (Day 10) visit for all other subjects. (see Section 12.5 for further details).

Subjects will be instructed to bring all bottles (including empty bottles) of study medication with them at these visits to assess medication compliance. Further details are available in Section 12.5.

14.17 Subject Diary Collection and Review

Subject diaries will be collected and reviewed at the TOC visit.

14.18 Pharmacokinetic Sample Collection

Blood samples for PK analysis will be drawn on Day 3 and Day 10 (±2) from the PK Subset only, which will consist of 10 subjects per treatment group (total of 60 subjects). On Day 3, samples will be collected at pre-dose (immediately before dosing) and at 2-6 hours' post-dose of either the morning or evening dose. On Day 10, a single PK sample will be collected. For the PK Subset, the Day 10 (TOC) visit must occur as close to Day 10 as possible. This sample may be collected at any time of the day.

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 will be described in the PK Manual.

14.19 Vital Signs

Vital signs, including blood pressure (systolic and diastolic), heart rate, respiratory rate and body temperature will be measured at the Screening and TOC visits, as well as at unscheduled visits, if needed.

14.20 Prior and Concomitant Medication Review

All medications (including prescription and over-the-counter medications, supplements and herbal products) taken from 28 days before Baseline (Day1) and through the TOC visit will be recorded on the eCRF. Only the use of antifungal medications, antibiotics for any reason or any other medication to treat an AE will be recorded after the TOC visit through the last study visit (FU). Start and stop dates of concomitant medications taken during antifungal therapy will be recorded on the eCRF. Prior and concomitant medications will be reviewed and recorded at all study visits.

See Section 13.0 for prohibited medications, medications to be administered with caution and further details for non-study treatments.

14.21 Adverse Event Monitoring

AEs will be recorded and reviewed at all scheduled on-site and phone-contact visits, as well as at all unscheduled study visits, from the time the ICF is signed. See Section 16.0 for further reference.

15.0 Study Schedule

Detailed schedules of all study visits and procedures are presented in Schedule of Visits and Procedures (Table 2).

Table 2: Schedule of Visits and Procedures (Study SCY-078-204)

Visit	V1 Screening[a]	V2 Baseline[a]	V3		V4 TOC	V5 Follow-up	Unscheduled Visits
			On-site (for PK subset only)	Phone contact (for non-PK subjects)			
Day (allowable window)	**D-1 (-2)**	**D1**	**D3**	**D3 (+3)**	**D10 (±2)**	**D25 (+4)**	
Study Procedures							
Informed consent	X						
Assignment of Subject ID number	X						
Inclusion/exclusion criteria	X	X					
Medical history and demographics	X						
Abbreviated physical exam	X				X		
Urine pregnancy test[b]	X						If needed
Safety labs[c]	X				X		If needed
Vulvovaginal sample for other pathogens[d] and pH	X						If needed
Vulvovaginal sample for KOH[e]	X				X	X	If needed
Vulvovaginal sample for fungal culture[e]	X				X	X	If needed
Rating of vulvovaginal signs by the investigator	X				X	X	X
Rating of vulvovaginal symptoms by the subject	X	X ---------- X				X	X
Randomization		X					
Study drug and subject diary dispensing		X					
Study drug dosing		X ---------- X					
Subject diary completion		X---------- X					

Visit	V1 Screening[a]	V2 Baseline[a]	V3		V4 TOC	V5 Follow-up	Unscheduled Visits
			On-site (for PK subset only)	Phone contact (for non-PK subjects)			
Day (allowable window)	**D-1 (-2)**	**D1**	**D3**	**D3 (+3)**	**D10 (±2)**	**D25 (+4)**	
Study Procedures							
Treatment compliance evaluation and study drug collection			X[g]	X[f]	X		
Subject diary collection					X		
PK sample collection[g]			X		X		
Vital signs	X				X		If needed
Prior & concomitant medication review	X	X	X	X	X	X	X
AE monitoring	X	X	X	X	X	X	X

Abbreviations: AE=adverse event; D=day; EOT=end of treatment; PK=pharmacokinetic; TOC=test of cure; V=visit

a. The Screening and Baseline visits may be combined.
b. Results will be reviewed at Baseline (Day 1) before starting/dispensing study drug .
c. Hematology and blood chemistry. Laboratory safety testing will be performed by a qualified central laboratory at Screening, TOC visit and at unscheduled visits if needed.
d. Analysis of samples for other pathogens will be done by a qualified laboratory and will include causative agents for bacterial vaginosis and *Trichomonas vaginalis*. Analysis of samples for other pathogens such as *Chlamydia trachomatis*, *Neisseria gonorrhoeae* or *Herpes* simplex may be performed if suspected.
e. Vaginal samples for KOH testing will be assessed locally; vaginal samples for fungal cultures, species identification and susceptibility will assessed by the central laboratory.
f. Treatment compliance will be reviewed at the Day 3 and TOC (Day 10) visits. PK subjects who have completed study drug dosing at the time of their Day 3 visit may have study drug collected on Day 3. Study drug will be collected at the TOC (Day 10) visit for all other subjects.
g. Blood samples for PK analysis will be drawn on Day 3 and Day 10 (±2) from the PK Subset only (10 subjects per treatment group [total of 60 subjects]). On Day 3, samples will be collected pre-dose (immediately before dosing) and at 2-6 hours' post-dose of either the morning or evening dose. On Day 10, a single PK sample will be collected. For the PK Subset, the Day 10 (TOC) visit must occur as close to Day 10 as possible. This sample may be collected at any time.

16.0 Safety Assessments and Monitoring

16.1 Definition of an Adverse Event

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

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

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

16.2 Definition of a Serious Adverse Event

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

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

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

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

16.3 Events of Clinical Interest

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

- ALT or AST > 8 x the upper limit of normal (ULN), confirmed by repeat testing
- ALT or AST > 5 x ULN for more than 2 weeks if new compared to Baseline, confirmed by repeat testing
- ALT or AST > 3 x ULN **and** either total bilirubin >2 x ULN or international normalized ratio (INR) >1.5 if new compared to Baseline, confirmed by repeat testing
- ALT or AST > 3 x ULN, confirmed by repeat test, with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

16.4 Overdose

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

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

16.5 Pregnancy

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

16.6 Unexpected Adverse Event

An AE is considered “unexpected” if it is not listed in the 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.

16.7 Grading of Adverse Events

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

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

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

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

16.8 Causality Assessment

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

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

16.9 Adverse Event Collection Timeframe

All AEs and SAEs will be recorded from the time informed consent is obtained through the FU visit (end of study).

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.

16.10 Serious Adverse Event Reporting Requirements

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

16.11 Adverse Event and Serious Adverse Event Follow-up

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

16.12 Serious Adverse Event Reporting – Procedures for Investigators

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

If the EDC system is temporarily unavailable (>24 hours), the event, including the investigator-determined causality to study drug, should be reported via a paper back-up SAE form to Novella Safety Surveillance via (contact information, i.e., e-mail or fax will be available on the SAE form).

Upon return of the availability of EDC system, the SAE information must be entered into the EDC system as soon as possible. The SAE form within the EDC system must be updated within 24 hours of knowledge/receipt of SAE follow-up information.

16.13 Procedures for Emergency Unblinding

This is a double-blind, double-dummy study. The Investigator should only be unblinded if it is necessary to determine treatment of emergency. The study personnel responsible for the treatment assignment can provide the information necessary to unblind the investigator (evaluator), in case of an emergency. If the evaluator is unblinded, the reason for unblinding should be documented in the comment page of the eCRF.

17.0 Data Collection, Study Monitoring and Record Management

17.1 Data Collection and Reporting

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

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

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

17.2 Study Monitoring

Study progress will be monitored by the Sponsor or its representative as frequently as necessary to ensure adequate and accurate data collection, protocol compliance, and study conduct in accordance with accepted regulatory requirements. The PI must make all the

subject data available to the monitor for review during the planned site monitoring visits. Arrangements for monitoring visits will be made in advance, except in emergency cases.

17.3 Investigator Study Files

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

- original protocol and all amendments;
- signed agreement or protocol;
- signed and dated study staff roles and responsibilities log;
- copy of the current *curriculum vitae* of the PI and of all sub-investigators;
- IRB/EC membership list and all IRB/EC approvals for the protocol and amendments, informed consent documentation and all updates, advertisements, and written information provided to subjects; all IRB/EC correspondence; documentation that the 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.

17.4 Retention of Records

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

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

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

18.0 Analytical Plan

All statistical processing will be performed using SAS® version 9.3 or later, unless otherwise stated. All statistical tests will be two-sided and interpreted at a 5% significance level. The study is not powered for formal statistical comparisons.

Descriptive statistics (i.e., mean, standard deviation, median, minimum, maximum, etc.) will be provided for all continuous variables; frequencies and percentages will be tabulated for incidence and categorical variables. For parameters measured over time, observed values and changes from baseline will be described for each time point.

All analyses will be presented by treatment group. Unless otherwise stated, data will be analyzed as is with no imputation. No adjustment for multiplicity will be employed.

A Statistical Analysis Plan (SAP) describing all statistical analyses in detail will be provided as a separate document. The SAP will be finalized prior to unblinding of the study treatments.

18.1 Sample Size Determination

This is an exploratory study and no formal sample size calculation was performed. Approximately 180 subjects will be enrolled and randomized in an equal allocation (at a 1:1:1:1:1:1 ratio) to the six study treatment groups (see Table 1). Thirty subjects per group are estimated to be adequate to perform an initial assessment of the safety and tolerability as well as the potential efficacy of SCY-078 in subjects with AVVC.

18.2 Analysis Populations

Intent-to-Treat (ITT) Population: All randomized subjects.

Modified Intent-to-Treat (mITT) Population: All randomized subjects who have a positive KOH test and a confirmed positive mycological culture for yeast at Baseline.

Per-Protocol (PP) Population: All mITT subjects who have completed the study drug treatment, who have a TOC evaluation AND who have no major protocol deviations.

PK Population: All randomized subjects who received study drug and provided at least one PK sample.

Safety Population: All randomized subjects who received at least one dose of study drug and who have at least one post-Baseline evaluation.

18.3 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 randomized, number completing the study, and reasons for discontinuation will be summarized by treatment group. Subject demographics and baseline characteristics such as age, race, ethnicity, sex, weight, height, body mass index, region (if applicable) and other relevant parameters will be tabulated by treatment group.

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.

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

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

18.5 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 by treatment group. 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.

18.6 Pharmacokinetics

18.6.1 Pharmacokinetic Assessments

Blood samples to measure SCY-078 and possible metabolite plasma concentrations will be drawn on Day 3 and Day 10 (±3) from the PK Subset, which will consist of 10 subjects per treatment group (total of 60 subjects). On Day 3, samples will be collected at pre-dose (immediately before dosing) and at 2-6 hours' post-dose of either the morning or evening study drug dose. On Day 10, a single PK sample will be collected. For the PK Subset, the Day 10 (TOC) visit must occur as close to Day 10 as possible. This sample may be collected at any time. Blood will be collected from all six treatment groups to keep the treatment blinding but only samples from subjects assigned to SCY-078 will be analyzed for PK.

18.6.2 Pharmacokinetic Analyses

PK parameters will be estimated using Population PK analysis in NONMEM as detailed in the SAP. The PK analyses will be done using the PK Population.

An evaluation of exposure for each dosing regimen relative to clinical cure will be performed.

The concentration versus time data from the PK samples collected in this study will be analyzed using a Population PK (Pop PK) model to predict AUC and C_{max} (as appropriate). A Pop PK modeling strategy is required because the sampling time points will not support a standalone PK analysis, and hence, the data from this study will be pooled with data from other oral studies to predict AUC and Cmax on Day 1 of treatment. A stand-alone Population PK report will prepared to describe the analysis performed on the PK samples collected from this study.

Further analysis of possible metabolites may be performed.

18.7 Efficacy

18.7.1 Efficacy Assessments

The primary efficacy endpoint of the study is the percentage of subjects with clinical cure (complete resolution of signs and symptoms) at the TOC visit. Secondary efficacy endpoints include the percentage of subjects with mycological eradication (negative fungal culture) at the TOC visit, the percentage of subjects with both clinical cure and mycological eradication at the TOC and FU visits, the percentage of subjects with continued clinical

response (continued absence of signs and symptoms) at the FU visit and the time to resolution of signs and symptoms after initiation of study drug. The percentage of subjects with a negative KOH test at the TOC visit, the percentage of subjects who are free of signs and symptoms at the FU visit, the percentage of subjects by *Candida* species infection at Baseline, the percentage of isolates susceptible to SCY-078 and fluconazole, the percentage of subjects with clinical cure (complete resolution of signs and symptoms) at TOC by *Candida* species and the percentage of subjects with mycological eradication (negative fungal culture) at TOC by *Candida* species will be evaluated as exploratory endpoints.

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

Clinical Outcome

- Clinical cure: Complete resolution of signs and symptoms of vulvovaginal infection without need for further antifungal treatment. Specifically, for complete resolution, any sign or symptom should be absent (score = 0) by the TOC visit.
- Clinical failure: No response to therapy or incomplete resolution of signs and symptoms or need for additional vulvovaginal or systemic antifungal therapy. If the subject receives or self-administers topical drug therapy for the treatment of vulvovaginal irritation/pruritus such as topical analgesic or corticosteroid after completing treatment with the study drug and before the TOC visit, the subject is considered a clinical failure.
- Continued Clinical Response: Continued absence of signs and symptoms of vulvovaginal infection at the FU visit in subjects who achieved clinical cure at the TOC visit.
- Free of Signs and Symptoms: Absence of signs and symptoms of vulvovaginal infection at the FU visit.
- **Mycological Outcome**
- Mycological eradication: A subject with negative culture (no growth) for *Candida* species.
- Mycological persistence: A subject with a positive culture for *Candida* species.

18.7.2 Efficacy Analyses

The efficacy analyses will be conducted using the mITT (primary analysis population), ITT and PP populations. The efficacy parameters will be evaluated comparing each SCY-078 treatment group (and all treatment groups combined) versus the active comparator (fluconazole) group.

The primary endpoint (clinical cure at TOC) will be analyzed using a Cochran-Mantel-Haenszel row mean scores test. Pairwise treatment comparisons of SCY-078 vs. fluconazole will be performed using a Fisher's Exact test; p-values and 95% confidence intervals will be presented. Subjects whose results are missing at Day 10 (TOC) will be imputed as failures in the analysis. A sensitivity analysis will be performed where subjects with missing values will be removed from the analysis.

For continuous efficacy endpoints, the Student's t-test will be used for pairwise treatment comparisons of SCY-078 vs. fluconazole; p-values and 95% confidence intervals will be presented for the differences between treatment groups. For categorical endpoints, Fisher's Exact test will be performed, and p-values and 95% confidence intervals will be presented. The time to resolution of signs and symptoms after initiation of study drug will be analyzed using Kaplan-Meier methods.

18.8 Safety

18.8.1 Safety Assessments

Safety will be evaluated throughout the study, including the following parameters: AEs, physical examination, vital signs, safety laboratory tests and treatment discontinuations.

Safety procedures are described in Section 14.0 and safety assessments are described in Section 16.0.

18.8.2 Analyses

Safety analyses will be conducted using the safety population.

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

Safety laboratory evaluations and vital signs will be summarized as observed values and as changes from baseline. In addition, shifts (with respect to the reference range) from baseline will be presented by treatment group for laboratory tests.

19.0 Ethics and Protection of Human Patients

19.1 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, the ethical principles established by the Declaration of Helsinki (as amended in Fortaleza, Brazil, October 2013), the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines, the 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.

19.2 Institutional Review Board/Ethics Committee Review

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

19.3 Informed Consent

The ICH issued guidelines to provide protection for human subjects in clinical investigations. The ICH Tripartite Guideline for 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 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 her signed subject ICF. In addition, the PI, or his or her designee, must document in the case history that informed consent was obtained before study participation.

19.4 Future Use of Samples

Biological samples collected during the study, including *Candida* spp. isolates (see Section 14.8 and Section 14.9) and plasma samples (see Section 14.18) may be maintained

in repositories for potential future use. Future research of *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.

19.5 Subject Privacy and Subject Confidentiality

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

19.6 Study Termination

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

19.7 Financial Disclosure

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

20.0 References

1. Sobel, JD. Vaginal candidosis. Lancet 2007;369:1961–71.
2. Hurley R, De Louvois J. Candida vaginitis. Postgrad Med J 1979;55:645–47.
3. Foxman B, Marsh JV, Gillespie B, Sobel JD. Frequency and response to vaginal symptoms among white and African American women: results of a random digit dialing survey. J Womens Health 1998;7:1167–74.
4. Berg AO, Heidrich FE, Fihn SD, et al. Establishing the cause of genitourinary symptoms in women in a family practice. Comparison of clinical examination and comprehensive microbiology. JAMA 1984; 251:620–25.
5. Eckert LO, Hawes SE, Stevens CE, Koutsky LA, Eschenbach DA, Holmes KK. Vulvovaginal candidiasis: clinical manifestations, risk factors, management algorithm. Obstet Gynecol 1998; 92: 757–65.
6. Diflucan prescribing information. Pfizer. Revised November 2014.
7. Larkin E, Hager C, Chandra J, Mukherjee PK, Retuerto M, Salem I, Long L, Isham N, Kovanda L, Borroto-Esoda K, Wring S, Angulo D, Ghannoum M. The Emerging Candida auris: Characterization of Growth Phenotype, Virulence Factors, Antifungal Activity, and Effect of SCY-078, a Novel Glucan Synthesis Inhibitor, on Growth Morphology and Biofilm Formation. Antimicrob Agents Chemother. 2017 Feb 21.
8. Sobel JD, Management of recurrent vulvovaginal candidiasis: unresolved issues. Curr Infect Dis Rep. 2006 Nov;8(6):481-6.
9. Vulvovaginal Candidiasis: Developing Drugs for Treatment – Guidance for Industry. FDA. Revised July 2016

21.0 Appendices

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

Prohibited Medications

The use of any topical vaginal corticoids and contraceptives is prohibited during the study. No antifungal treatment other than the study drug is allowed during the study. In addition, the medications listed below are also prohibited.

Strong 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] Time-dependent inhibitors[a] • clarithromycin • ritonavir • saquinavir	Reversible inhibitors[b] • fluconazole[c]	• avasimibe • carbamazepine • phenytoin • rifampin • St. John's wort

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 and 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.

CYP2C8 substrates

CYP	Substrates
2C8[a]	amiodarone, amodiaquine, paclitaxel, repaglinide, montelukast, pioglitazone and rosiglitazone,

a. The CYP2C8 substrates listed in this table are not permitted during the 48 hours prior to enrollment or during study treatment.

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 or during study treatment

Medications to be administered with Caution and Monitored as Appropriate

CYP	Moderate Inhibitors
3A4/5	Reversible inhibitors[a] • 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 ration

OATP1B3 substrates

OATP	Substrate
1B3	*In vitro*, SCY-078 is an inhibitor of the OATP1B3 liver uptake transporter. The clinical significance of this inhibition is unknown; however, there is a potential risk for increased exposure of the concomitant medications (arising from lowered hepatic clearance) when administering SCY-078 with drugs known to be OATP1B3 selective substrates. Therefore, caution should be exercised when administering SCY-078 with drugs known to be OATP1B3 selective substrates such as telmisartan, including monitoring the subject for signs of overexposure associated with the concomitant medications as described in the product prescribing information.

Sources:

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

Appendix B: Vulvovaginal Signs and Symptoms Scale

SIGNS:

To be rated by the investigator during the vulvovaginal examination

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

Definitions:

Absent: none

Mild: slight

Moderate: definitely noticeable

Severe: marked, intense

SYMPTOMS:

To be rated by the subject

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

Definitions:

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

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

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

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