SCYNEXIS, Inc.

Clinical Trial Protocol

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Oral Ibrexafungerp (SCY-078) vs. Placebo in Subjects with Acute Vulvovaginal Candidiasis

SCYNEXIS Protocol Number SCY-078-303

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2.0 Protocol Approvals

PROTOCOL ID: SCY-078-303

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Oral Ibrexafungerp (SCY-078) vs. Placebo in Subjects with Acute Vulvovaginal Candidiasis

SCYNEXIS, Inc. Approval:

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Investigator Agreement Statement

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A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Oral Ibrexafungerp (SCY-078) vs. Placebo in Subjects with Acute Vulvovaginal Candidiasis

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

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

Principal Investigator's Signature	Date

Principal Investigator's Name (Printed)

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3.0 Revision History

Not applicable

4.0 Abbreviations

ABBREVIATION	DEFINITION
AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
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
CMH	Cochran Mantel Haenszel
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
EDC	electronic data capture
FDA	Food and Drug Administration
FLU	fluconazole
FU	follow-up
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GSI	glucan synthesis inhibitor

ABBREVIATION	DEFINITION
IB	Investigator´s Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ID	identification
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
KOH	potassium hydroxide
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
mITT	modified intent to treat
OATP1B3	organic anion-transporting polypeptide 1B3
P-gp	P-glycoprotein
PI	principal investigator
PP	per protocol
QD	once daily
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOC	standard of care
TOC	test of cure
ULN	upper limit of normal
US	United States
VSS Scale	Vulvovaginal Signs and Symptoms Scale
VVC	vulvovaginal candidiasis

ABBREVIATION	DEFINITION
WBC	white blood cell

5.0 Protocol Synopsis

Title: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Oral Ibrexafungerp (SCY-078) vs. Placebo in Subjects with Acute Vulvovaginal Candidiasis

Primary Objectives:

- To evaluate the efficacy of oral ibrexafungerp versus placebo in subjects with acute vulvovaginal candidiasis (AVVC) by comparing the clinical outcomes of ibrexafungerp and placebo

Secondary Objectives:

- To evaluate the efficacy of oral ibrexafungerp versus placebo in subjects with AVVC based on mycological and clinical outcomes
- To evaluate the safety and tolerability of oral ibrexafungerp versus placebo 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 culture for growth of *Candida* species) at the TOC visit
- The percentage of subjects with clinical cure and mycological eradication (responder outcome) at the TOC visit.
- The percentage of subjects with complete resolution of symptoms at the Follow-up (FU) visit.
- The percentage of subjects with clinical improvement (partial or complete resolution of signs and symptoms with total composite score no greater than 1) at the TOC visit.
- The absolute change in signs and symptoms score from Baseline to TOC and FU visits.

Safety and tolerability as measured by:

- Adverse events (AEs), vital signs, physical examination, treatment discontinuation and safety laboratory tests.

Study Phase: 3

Study Design: This is a Phase 3, randomized, multicenter, double-blind, placebo-controlled study to evaluate the efficacy and safety of oral Ibrexafungerp (SCY-078) compared to placebo in female subjects 12 years and older with AVVC. Approximately 366 eligible subjects will be enrolled and randomized in a 2:1 ratio to either ibrexafungerp (300-mg dose twice a day [BID]) or matching placebo administered BID for 1 day.

Study Visits

The study will consist of a Screening visit, a Baseline visit on Day 1 (these visits may occur on the same day), a TOC visit on Day 11 (±3) and a FU visit on Day 25 (±4).

Screening

At Screening, subjects who are experiencing vulvovaginal symptoms will be evaluated by the investigator, who will obtain a vaginal sample for potassium hydroxide (KOH) testing and vaginal pH determination by the local laboratory prior to randomization and initiation of treatment. The vaginal samples will also be evaluated locally for findings indicative of bacterial vaginosis and *Trichomonas vaginalis*. A vaginal sample for fungal culture and for species identification and susceptibility testing will be obtained and sent to a designated central laboratory. If the investigator suspects *Herpes* virus, *Neisseria gonorrhoeae or Chlamydia trachomatis* infection, a vaginal sample will be collected and sent to a designated central laboratory. The investigators and the subjects will rate the signs and symptoms 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 ≥4 with at least 2 signs or symptoms having a score of 2 (moderate) or greater in the VSS Scale at Baseline, a positive KOH test and a normal vaginal pH (≤4.5).

The Screening and Baseline (Day 1) visits may occur on the same day.

Baseline

Eligible subjects will be randomized in a 2:1 ratio to one of the following two treatment groups:

- Oral ibrexafungerp 300-mg dose BID for 1 day
- Oral ibrexafungerp matching placebo BID for 1 day

For the purpose of maintaining treatment blinding, all subjects randomized to the placebo group will receive matching ibrexafungerp placebo tablets. Subjects will receive their first dose of study drug at the site and will be dispensed study drug and subject diaries to rate their vulvovaginal symptoms of infection and to record dosing details, AEs and concomitant medication use from Day 1 until the TOC visit (Day 8-Day 14). Subjects will self-administer their second study drug dose at home 12 hours after the first dose.

Assessment of Clinical Cure (TOC)

At the TOC visit (Day 8-Day 14), subjects will return any remaining medication as well as empty bottles of the study drug and treatment compliance will be evaluated. Subject diaries will be returned and reviewed. The investigators and the subjects will rate the signs and symptoms of infection, respectively, on the VSS Scale. A vaginal sample for fungal culture and for species identification and antifungal susceptibility testing will be obtained and sent to a designated central laboratory. An abbreviated physical exam, vital signs measurements and safety laboratory tests will also be performed.

If the baseline vulvovaginal symptoms have not noticeably improved or have worsened and the investigator considers that rescue antifungal medication may be needed, a vaginal sample should also be obtained for KOH testing by the local laboratory.

Follow up

At the FU visit, subjects will rate their symptoms of infection on the VSS Scale. Vulvovaginal samples for KOH testing and fungal culture should be obtained if there is persistence or recurrence of vulvovaginal symptoms. Only if symptoms are present, the investigator will perform a vulvovaginal examination to rate the subject´s signs of infection.

All Visits

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

Efficacy (Clinical and Mycological) and Safety Assessments

Clinical Evaluation

The signs (edema, erythema and excoriation or fissures) and symptoms (burning, itching and irritation) of infection will be assessed by the investigator and the subject, respectively, on the VSS Scale [provided in Appendix B of the protocol]). 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 visit or FU visit if symptoms persist or recur. Vaginal samples will be collected at Screening, TOC visit and prior to the initiation of rescue antifungal medication during the study for fungal cultures and tested centrally. The central lab will determine growth of yeasts, species identification and susceptibility testing.

Safety Assessments

Safety procedures will include collection of AEs, treatment discontinuations, physical examination, vital signs, safety laboratory tests and prior and concomitant medications.

Early Termination

If the subject experiences persistence or worsening or recurrence of symptoms that per the investigator's assessment (e.g., symptoms ≥3) warrant the use of rescue antifungal therapy, a vaginal examination with investigator's rating of signs should be completed. Additionally, vulvovaginal samples should be obtained for KOH testing and pH measurements by the local laboratory, fungal culture by the central laboratory and investigation of other pathogens such as bacterial vaginosis and *Trichomonas vaginalis* by the local laboratory. If the KOH test is negative, the investigator should consider other causes for the persistence or worsening of the symptoms and antifungal rescue medication may not be indicated.

If the investigator's rating of the vulvovaginal signs and vaginal sample collection is not possible prior to the initiation of the rescue therapy, it should still be completed as soon as possible after rescue therapy is initiated.

In addition to the vaginal examination, the symptoms that led to the use of rescue antifungal therapy should be documented in the eCRF and the following procedures should also be completed:

- If rescue therapy is administered prior to or at the TOC visit, all TOC visit procedures should be completed and no additional visits will be needed. The subject will be considered as early termination due to lack of efficacy prior to or at TOC.

- If rescue therapy is administered after the TOC visit but prior to or at the FU visit, all FU visit procedures should be completed and no additional visits will be needed. The subject will be considered as early termination due to lack of efficacy after TOC but prior to or at FU.

Oral fluconazole [one 150-mg dose] may be provided to study sites as rescue medication. However, at the investigator's discretion other approved antifungal agents may be administered as rescue medication to a particular patient for whom fluconazole is not considered the optimal option. All rescue antifungal medications should be documented in the eCRF.

Target Population: The study population will include female subjects 12 years and older with AVVC.

KEY Inclusion Criteria:

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

1. Subject is a postmenarchal female subject 12 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. Minimum composite vulvovaginal signs and symptoms score of $\geq$4 with at least 2 signs or symptoms having a score of 2 (moderate) or greater in the VSS Scale at Baseline
    b. Positive microscopic examination with 10% KOH in a vaginal sample collected at Screening revealing yeast forms (hyphae/pseudohyphae) or budding yeasts
    c. Normal vaginal pH ($\leq$4.5)
3. Subject is able to take oral tablets.

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 vaginalis, Herpes* virus, *Neisseria gonorrhoeae, Chlamydia trachomatis*, symptomatic human papillomavirus or other mixed infections.
2. Subject received systemic and/or topical (vaginal) antifungal treatment, including prescription or over-the-counter products, within 28 days of the Baseline visit.
3. Subject has active menstruation at the Baseline visit.
4. Subject has uncontrolled diabetes mellitus.
5. Subject has a history of or an active cervical/vaginal cancer.
6. 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) of the protocol, 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. Select strong CYP3A4/5 inhibitors and CYP3A4/5 inducers during the 7 days prior to enrollment and during study treatment until the TOC visit
    c. Select P-gp substrates during the 48 hours prior to enrollment or during study treatment with SCY-078

Study Drugs: Study drug will consist of ibrexafungerp (SCY-078) (150-mg tablets) and ibrexafungerp matching placebo tablets. Study drug will be provided by the Sponsor.

Ibrexafungerp 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.

The placebo product matching SCY-078 will be supplied as a tablet matching the size and appearance of the active tablet. The tablet formulation contains silicified microcrystalline cellulose, crospovidone, mannitol, colloidal silicon dioxide, magnesium stearate (non-bovine) and butylated hydroxyanisole.

Study Treatment Groups:

Subjects who meet all of the inclusion and none of the exclusion criteria will be enrolled into the study and will be randomized in a 2:1 ratio to either oral ibrexafungerp or ibrexafungerp matching placebo, as follows:

- Oral ibrexafungerp 300-mg dose BID for 1 day
- Oral ibrexafungerp matching placebo BID for 1 day

Subjects will receive their first dose of study drug at the site and will be dispensed the second dose for self-administration at home 12 hours after the first dose.

Study Blinding, Randomization and Stratification: This is a randomized, double-blind study. All site and sponsor personnel will be blinded to treatment assignment.

Approximately 366 eligible subjects will be enrolled and randomized in a 2:1 ratio to one of the two study treatment groups. For the purpose of maintaining treatment blinding, all subjects randomized to the placebo group will receive matching ibrexafungerp placebo tablets. All randomization of subjects will be managed electronically through an interactive response system (voice or web-based).

Eligible subjects will be stratified at randomization based on the presence or absence of a diagnosis of diabetes mellitus (diabetes mellitus: YES or NO).

Study Evaluations:

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 the percentage of subjects with mycological eradication (negative culture for growth of *Candida* species) at the TOC visit, the percentage of subjects with clinical cure and mycological eradication at the TOC visit, the percentage of subjects with complete resolution of symptoms at the FU visit, and the percentage of subjects with clinical improvement (partial or complete resolution of signs and symptoms with a total composite score no greater than 1) at the TOC visit.

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.

Mycological Outcome

- Mycological eradication: A subject with negative culture 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, treatment discontinuations, physical examination, vital signs, safety laboratory tests, and prior and concomitant medications.

AEs will be recorded and reviewed at all scheduled and unscheduled study visits from the time the Informed Consent Form is signed. An abbreviated physical examination, including general appearance and an overall examination of body systems, will be conducted at Screening and at

the TOC visit. Vital signs, including blood pressure (systolic and diastolic), heart rate, respiratory rate and body temperature will be measured at the Screening and TOC visits, and at unscheduled visits, if needed. Safety laboratory tests (hematology and blood chemistry) will be measured at Screening, at the TOC visit and at unscheduled visits, if needed. All prior and concomitant medications taken before Baseline (Day 1) through the TOC visit will be recorded. Only the use of antifungal medications, vaginal (topical) medications, antibiotics for any reason or any other medications to treat an AE will be recorded after the TOC visit through the last study visit (FU).

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.

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

The clinical cure and mycological eradication rates will be described by baseline *Candida* species, when the number of isolates per species allows.

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

The primary endpoint of the study is the percentage of subjects achieving a clinical cure at the TOC visit. Assuming clinical cure rates of 50% and 30% for ibrexafungerp and placebo administered in a 2:1 ratio, respectively, approximately 282 subjects will provide 90% power to detect a difference between ibrexafungerp and placebo based on a Pearson's Chi-squared test with a Type 1 error rate of 5%. Because it is expected that approximately 20% of subjects may not have a mycological culture-confirmed infection at Baseline and approximately 10% may withdraw early from the study, an additional 84 subjects are added for a total of 366 subjects (244 subjects randomized to ibrexafungerp and 122 subjects, to placebo).

Analysis Populations

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

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

Modified Intent-to-Treat (mITT) Population: All randomized subjects who have a positive culture for *Candida* species at Baseline.

Per-Protocol (PP) Population: All mITT subjects who have completed the study drug treatment AND who have a TOC evaluation.

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

Efficacy Analyses:

The efficacy analyses will be conducted using the mITT (primary analysis population), ITT and PP populations to evaluate SCY-078 vs. placebo.

The primary endpoint, percentage of subjects with clinical cure at TOC, will be analyzed using a Cochran Mantel Haenszel (CMH) test adjusted for site; the p-value and 95% confidence intervals will be presented. Missing Day 8-Day 14 (TOC) data for the primary endpoint 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. All other data will be analyzed as is with no imputation.

For other continuous efficacy endpoints, a two-way analysis of variance (ANOVA) model will be used including effects for treatment and site; p-values and 95% confidence intervals will be presented. For other categorical endpoints, the CMH test adjusted for site will be performed, and p-values and 95% confidence intervals will be presented.

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 laboratory tests.

6.0 Schematic of Study Design

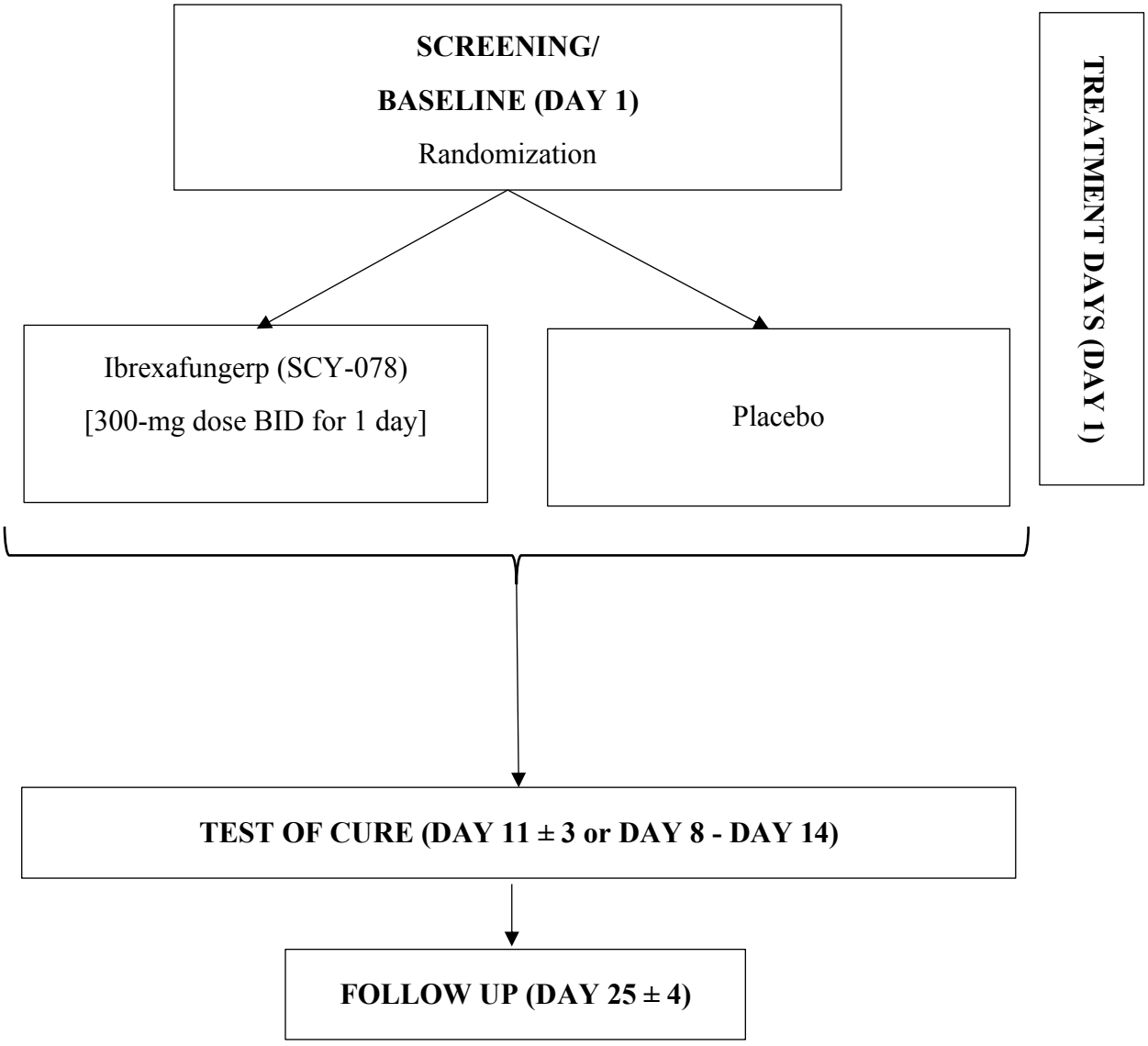

Figure 1 Schematic of Study Design

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]

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[4,5]. 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 provide evidence of the efficacy and evaluate the safety of oral 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 ibrexafungerp (formerly known as SCY-078)

Ibrexafungerp (formerly known as SCY-078) is a member of a new class of antifungal agents and is an orally active, semi-synthetic, triterpenoid derivative of the natural product enfumafungin. Ibrexafungerp (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 ibrexafungerp (SCY-078) has *in vitro* fungicidal activity against *Candida* spp. isolates similar to that observed with the echinocandins.

Ibrexafungerp (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 ibrexafungerp (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)[6] and European Committee on Antimicrobial Susceptibility Testing methods. Overall, the epidemiological studies have demonstrated that ibrexafungerp (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 ibrexafungerp SCY-078 for the treatment of invasive fungal infections.

Activity against *Candida* spp.

Ibrexafungerp (SCY-078) has been evaluated against >2000 *Candida* isolates, including all clinically relevant species with more than 300 *C. albicans, more than* 300 *C. glabrata* and more than 100 *C. auris* isolates tested. These *in vitro* studies have demonstrated the broad spectrum of anti-*Candida* activity of SCY-078. Additionally, ibrexafungerp (SCY-078) demonstrated *in vitro* activity against pre-formed biofilms, which is a relevant feature when addressing catheter-related *Candida* infections and, potentially, VVC. Studies conducted with azole- and echinocandin-resistant strains have shown that ibrexafungerp (SCY-078) retains activity (i.e., no significant change in minimum inhibitory concentration [MIC] compared to wild type) against >90% of azole-resistant strains and >70% of *Candida* strains with *FKS* mutations commonly associated with echinocandin resistance. Interestingly, although ibrexafungerp (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.

Ibrexafungerp (SCY-078) was evaluated *in vitro* against clinical isolates of echinocandin-resistant strains of *Candida* spp. containing mutations in the *FKS* gene. Overall, ibrexafungerp (SCY-078) was active against the majority of the echinocandin-resistant strains tested. Significantly, ibrexafungerp (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 ibrexafungerp (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, ibrexafungerp (SCY-078) did not select for mutations at positions S663 or S645. These results suggest that ibrexafungerp (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, ibrexafungerp (SCY-078) was active against >70% of these isolates. ibrexafungerp (SCY-078) has also demonstrated a potent activity against life-threatening and multi-drug-resistant *C. auris* strains over 100 different *C. auris* isolates, at concentrations indicative of potential clinically relevant effect. *C. auris* has been recently highlighted as a clinical alert by the Centers for Disease Control and Prevention (CDC) because of the global emergence of this fungal infection with limited therapeutic options and high mortality.

Activity against *Aspergillus* spp.

The *in vitro* activity of ibrexafungerp (SCY-078) has been evaluated against >450 clinical *Aspergillus* isolates, including most clinically relevant species and azole-resistant strains. The results demonstrated potent activity of ibrexafungerp (SCY-078) against all of the strains tested.

Murine models of invasive fungal infections

The antifungal efficacy of ibrexafungerp (SCY-078) has been evaluated in several murine models of disseminated candidiasis and aspergillosis. In a disseminated *C. albicans* model, ibrexafungerp (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 ibrexafungerp (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 ibrexafungerp (SCY-078) following oral administration for up to 90 days. Reproductive and developmental toxicity studies have also been completed. The results from the non-clinical safety program provide adequate safety support for the doses and treatment duration intended in this study.

The *in vitro* studies indicated that ibrexafungerp (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 ibrexafungerp (SCY-078); therefore, the concurrent administration of ibrexafungerp (SCY-078) with such inhibitors is prohibited.

Clinical experience

To date, over 500 subjects and patients have received either oral or IV formulations of ibrexafungerp (SCY-078) in Phase 1 and Phase 2 studies.

Ibrexafungerp (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 ibrexafungerp (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 ibrexafungerp (SCY-078) or fluconazole. Ibrexafungerp (SCY-078) was well tolerated, with an AE profile typical of this population and comparable to the Standard of Care (SOC). The results from this study also indicated that the higher dose of ibrexafungerp (SCY-078) tested (750 mg once daily [QD]) is predicted to achieve the target exposure at steady state in the majority of patients.

A Phase 2 proof-of-concept study (SCY-078-203) of oral ibrexafungerp (SCY-078) in patients with acute vulvovaginal candidiasis (AVVC) has also been completed. In this multicenter, randomized, active-controlled, evaluator-blinded study of oral ibrexafungerp (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 ibrexafungerp (SCY-078) 750 mg with a 1250 mg loading dose for three days, oral ibrexafungerp (SCY-078) 750 mg with a 1250 mg loading dose for five days or a single dose of oral fluconazole. Ibrexafungerp (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.

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

The primary objective of the study was dose selection for our Phase 3 pivotal program in VVC. This Phase 2b study was a randomized, multi-center, double-blind, active-controlled, dose-finding study designed to evaluate the safety, efficacy, tolerability and pharmacokinetics of five dose regimens of oral ibrexafungerp (SCY-078) in patients with moderate-to-severe acute VVC (defined as signs and symptoms score of 7 or greater), with oral fluconazole (FLU) as a reference arm. The study enrolled a total of 186 patients and 153 patients were included in the culture-confirmed, modified, intent-to-treat population. The study was not intended, nor powered, to achieve statistically significant differences in any of the evaluated endpoints. The total doses tested ranged from 600 mg to 1800 mg and the durations explored were 1 or 3 days. The maximum duration of treatment of 3 days was based on our previous Phase 2a study, SCY-078-203, in which we showed that 3 days of treatment performed similarly to 5 days, so in the DOVE study we explored 3 days and a shorter treatment duration.

The primary efficacy endpoint was clinical cure, defined as complete resolution of all signs and symptoms at the Day 10 Test of Cure (TOC) visit without the need of additional antifungal therapy. Secondary endpoints included mycological eradication and composite endpoint including both clinical cure and mycological eradication. In this Phase 2 study, response was also evaluated as

the percentage of subjects achieving a noticeable improvement in their signs and symptoms by achieving a composite sign and symptoms score of 0 or 1, absolute change in signs and symptoms from baseline and need for rescue antifungal therapy.

All doses tested achieved meaningful clinical cure and mycological eradication rates and the dose that was considered to provide the best combination of attributes for this indication is the ibrexafungerp (SCY-078) 600-mg dose administered as 300 mg BID for 2 doses.

At Day 10, the TOC visit, the 600-mg dose showed clinical and mycological response rates in-line with the reference fluconazole arm. Specifically, the clinical cure was reported in 14 of 27 of patients (52%) in the 600-mg dose and in 14 of 24 of patients (58%) in the fluconazole arm. The percentage of patients showing 0 or 1 signs and symptoms score was also comparable, with 70% and 71% of patients reporting this improvement in the ibrexafungerp (SCY-078) 600-mg dose and fluconazole arms, respectively. The mycological eradication at this timepoint was 63% for both groups.

At Day 25, the follow-up (FU) visit, the ibrexafungerp (SCY-078) 600-mg dose showed a trend towards improved clinical and mycological outcomes when compared to the fluconazole arm. If patients had persistence or recurrence of signs and symptoms of VVC, rescue antifungal medication could be prescribed. Seven (7) patients treated with fluconazole received rescue antifungal medication, whereas one patient treated with ibrexafungerp (SCY-078) 600 mg received rescue antifungal medication. The rate of patients with zero signs and symptoms at the FU visit was 70% for the ibrexafungerp (SCY-078) 600-mg dose versus 50% for the fluconazole arm. A similar difference was observed with the "0 or 1 signs and symptoms score" analysis, with 82% of patients achieving this improvement with the ibrexafungerp (SCY-078) 600-mg dose versus 58% with fluconazole. The mycological eradication at this timepoint was also numerically higher in the 600-mg dose (48%) when compared to the fluconazole arm (38%).

Oral ibrexafungerp (SCY-078) 600-mg dose was generally well tolerated, with self-limiting (generally one-day duration), mild to moderate gastrointestinal adverse events (AEs) being the most commonly reported. Nausea was reported in three patients (10%) in the ibrexafungerp (SCY-078) 600-mg dose arm compared to two patients (6%) in the FLU arm. Diarrhea and loose stool was reported in five patients (17%) in the ibrexafungerp (SCY-078) 600-mg dose arm compared to one patient in the FLU arm (3%). Abdominal pain was reported in one patient (3%) in the ibrexafungerp (SCY-078) 600-mg dose arm compared to 5 patients (16%) in the FLU arm. No vomiting, severe AEs or discontinuations due to AEs were reported in the ibrexafungerp (SCY-078) 600-mg dose arm.

Several drug-drug interaction studies have been conducted. Ketoconazole (a strong inhibitor of CYP3A) induces a significant (5-fold) increase in ibrexafungerp (SCY-078) exposure, while diltiazem (a moderate inhibitor of CYP3A) induces a mild to moderate (<3-fold) increase in ibrexafungerp (SCY-078) exposure. Ibrexafungerp (SCY-078) did not have a clinically

meaningful 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.

Ibrexafungerp (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. SCY-078 through the remainder of this protocol will be referred to as ibrexafungerp from this point forward.

For additional information on ibrexafungerp, 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 one dosing regimen of ibrexafungerp as compared to placebo in female patients 12 years and older with acute vulvovaginal candidiasis (AVVC). The study design generally follows the FDA guidance regarding drug development for vulvovaginal candidiasis[7] .

Rationale for Study Indication and Population

Considering the properties of ibrexafungerp 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 AVVC are intended for this study to facilitate the identification of a clinically meaningful effect of ibrexafungerp in the intended population.

Rationale for Selected Dose Levels and Dosing Regimens

The ibrexafungerp selected dose of 300 mg BID for 1 day showed meaningful clinical and mycological response rates in a Phase 2b study (DOVE) with adequate tolerability. This dose is in the range of doses that have been well tolerated in Phase 1 investigations.

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 TOC visit on Day 8-Day 14, which is in line with the FDA guidance on vulvovaginal candidiasis[7]. The secondary efficacy endpoints will include mycological eradication (negative culture for growth of *Candida* spp.) at the TOC visit, a composite endpoint of both clinical cure and mycological eradication at the TOC visit, complete resolution of symptoms at the Follow-up (FU) visit on Day 25 (±4), which are also in line with current guidelines. Additional endpoints are evaluated, including clinical improvement (partial or complete resolution of signs and symptoms with total composite score no greater than 1) at the

TOC visit, since this is considered a meaningful clinical improvement. The safety and tolerability of ibrexafungerp will also be evaluated as secondary objectives.

Rationale for Study Design

This trial is being conducted as a randomized, placebo-controlled, double-blind study. This design is considered an appropriate design for this indication and phase of investigation and will use matching ibrexafungerp placebo. The placebo-controlled design for this study is in line with the current regulatory guidance and is appropriate considering that acute VVC is not a life threatening infection, that delayed treatment is not expected to result in a complication of the VVC and that subjects enrolled will be closely followed up to be provided rescue therapy, when indicated, after failure of the assigned study drug has been determined.

The data generated from this study will provide a characterization of the efficacy, safety and tolerability of ibrexafungerp in subjects with AVVC.

8.0 Study Objectives

8.1 Primary Objectives

- To evaluate the efficacy of oral ibrexafungerp versus placebo in subjects with acute vulvovaginal candidiasis (AVVC) by comparing the clinical outcomes of ibrexafungerp and placebo

8.2 Secondary Objectives

- To evaluate the efficacy of oral ibrexafungerp versus placebo in subjects with AVVC based on mycological and clinical outcomes
- To evaluate the safety and tolerability of oral ibrexafungerp versus placebo 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 test-of-cure (TOC) visit

9.2 Secondary Endpoints

Efficacy as measured by:

- The percentage of subjects with mycological eradication (negative culture for growth of *Candida* species) at the TOC visit
- The percentage of subjects with clinical cure and mycological eradication (responder outcome) at the TOC visit.
- The percentage of subjects with complete resolution of symptoms at the Follow-up (FU) visit.
- The percentage of subjects with clinical improvement (partial or complete resolution of signs and symptoms with total composite score no greater than 1) at the TOC visit.
- The absolute change in signs and symptoms score from Baseline to TOC and FU visits.

Safety and tolerability as measured by:

- Adverse events (AEs), vital signs, physical examination, treatment discontinuation and safety laboratory tests

10.0 Study Design

10.1 Overall Description of the Study

This is a Phase 3, randomized, multicenter, double-blind, placebo-controlled study to evaluate the efficacy and safety of oral ibrexafungerp compared to placebo in female subjects 12 years and older with AVVC.

Approximately 366 eligible subjects will be enrolled and randomized in a 2:1 ratio to either ibrexafungerp (300-mg dose twice a day [BID]) or matching placebo administered BID for 1 day.

The primary objective of this study is to evaluate the efficacy of oral ibrexafungerp in subjects with AVVC by comparing the clinical outcomes of ibrexafungerp and placebo.

The study will consist of a Screening visit, a Baseline visit on Day 1 (these visits may occur on the same day), a TOC visit on Day 11 (±3) and a FU visit on Day 25 (±4).

Efficacy and safety 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. Efficacy will also be assessed by the percentage of subjects with mycological eradication (negative culture for growth of *Candida* species) at the TOC visit, the percentage of subjects with both clinical cure and mycological eradication at the TOC visit, the percentage of subjects with complete resolution of symptoms at the FU visit and the percentage of subjects with clinical improvement (partial or complete resolution of signs and symptoms with total composite score no greater than 1) at the TOC visit. Safety and tolerability will be evaluated

throughout the study, including the following parameters: AEs, vital signs, an abbreviated physical examination, treatment discontinuations and safety laboratory tests.

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 [Day -2])

At Screening, subjects who are experiencing vulvovaginal symptoms will be evaluated by the investigator, who will obtain a vaginal sample for potassium hydroxide (KOH) testing and vaginal pH determination by the local laboratory prior to randomization and initiation of treatment. The vaginal samples will also be evaluated locally for findings indicative of bacterial vaginosis and *Trichomonas vaginalis*. A vaginal sample for fungal culture and for species identification and susceptibility testing will be obtained and sent to a designated central laboratory. If the investigator suspects *Herpes* virus, *Neisseria gonorrhoeae or Chlamydia trachomatis* infection, a vaginal sample will be collected and sent to a designated central laboratory. The investigators and the subjects will rate the signs and symptoms 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 ≥4 with at least 2 signs or symptoms having a score of 2 (moderate) or greater in the VSS Scale at Baseline, a positive KOH test and a normal vaginal pH (≤4.5).

The Screening and Baseline (Day 1) visits may occur on the same day.

Baseline (Day 1)

Eligible subjects will be randomized in a 2:1 ratio to one of the following two treatment groups:

- Oral ibrexafungerp 300-mg dose BID for 1 day
- Oral ibrexafungerp matching placebo BID for 1 day

For the purpose of maintaining treatment blinding, all subjects randomized to the placebo group will receive matching ibrexafungerp placebo tablets. Subjects will receive their first dose of study drug at the site and will be dispensed study drug and subject diaries to rate their vulvovaginal symptoms of infection and to record dosing details, AEs and concomitant medication use from Day 1 until the TOC visit (Day 8-Day 14). The second study drug dose will be self-administered by the subjects approximately 12 hours later at home on Baseline (Day 1). If administering the

first dose at the study center would complicate the administration of the second dose 12 hours later (e.g. first dose at 3 p.m. will require second dose at 3 a.m.), the subject can self-administer both doses at home to allow for a more convenient dosing schedule (e.g., 8 p.m. and 8 a.m.). Subjects will record study drug dosing details in their study diary.

Assessment of Clinical Cure (TOC [Day 11 ±3])

At the TOC visit (Day 8-Day 14), subjects will return any remaining medication as well as empty bottles of the study drug and treatment compliance will be evaluated. Subject diaries will be returned and reviewed. The investigators and the subjects will rate the signs and symptoms of infection, respectively, on the VSS Scale. A vaginal sample for fungal culture and for species identification and antifungal susceptibility testing will be obtained and sent to a designated central laboratory. An abbreviated physical exam, vital signs measurements and safety laboratory tests will also be performed.

If the baseline vulvovaginal symptoms have not noticeably improved or have worsened and the investigator considers that rescue antifungal medication may be needed, a vaginal sample should also be obtained for KOH testing by the local laboratory.

Follow up (Day 25 [±4])

At the FU visit, subjects will rate their symptoms of infection on the VSS Scale. Vulvovaginal samples for KOH testing and fungal culture should be obtained if there is persistence or recurrence of vulvovaginal symptoms. Only if symptoms are present, the investigator will perform a vulvovaginal examination to rate the subject´s signs of infection.

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 tolerability assessments.

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 culture for growth of *Candida* species) at the TOC visit, the percentage of subjects with clinical cure and mycological

eradication at the TOC visit, the percentage of subjects with complete resolution of symptoms at the FU visit, and the percentage of subjects with clinical improvement (partial or complete resolution of signs and symptoms with a total composite score no greater than 1) at the TOC visit and the absolute change in signs and symptoms score from Baseline to TOC and FU visits..

Clinical Evaluation

The signs (edema, erythema and excoriation or fissures) and symptoms (burning, itching 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 visit or FU visit if symptoms persist or recur. Vaginal samples will be collected at Screening, TOC visit and when possible vaginal samples will also be collected prior to the initiation of rescue antifungal medication during the study for central lab fungal cultures. The central lab will culture samples for the presences of yeast, and process isolates for species identification and susceptibility testing.

Safety Assessments

Safety procedures will include collection of AEs, treatment discontinuations, physical examination, vital signs, safety laboratory tests and prior and concomitant medications.

10.2 Blinding, Randomization and Stratification

This is a randomized, double-blind study. All site and sponsor personnel will be blinded to treatment assignment.

Approximately 366 eligible subjects will be enrolled and randomized in a 2:1 ratio to one of the two study treatment groups. For the purpose of maintaining treatment blinding, all subjects randomized to the placebo group will receive matching ibrexafungerp placebo tablets. All randomization of subjects will be managed electronically through an interactive response system (voice or web-based).

Eligible subjects will be stratified at randomization based on the presence or absence of a diagnosis of diabetes mellitus (diabetes mellitus: YES or NO).

10.3 Study Duration

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

10.4 Number of Centers

Approximately 30 study centers are expected to participate in subject enrollment and treatment.

11.0 Study Population

The study population will include female subjects 12 years and older with AVVC.

11.1 Inclusion Criteria

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

1. Subject is a postmenarchal female subject 12 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. Minimum composite vulvovaginal signs and symptoms score of $\geq$4 with at least 2 signs or symptoms having a score of 2 (moderate) or greater in the VSS Scale at Baseline
    b. Positive microscopic examination with 10% KOH in a vaginal sample collected at Screening revealing yeast forms (hyphae/pseudohyphae) or budding yeasts
    c. Normal vaginal pH ($\leq$4.5)
3. Subject is able to take oral tablets.
4. Subject is not pregnant or lactating 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) has undergone bilateral oophorectomy and/or hysterectomy or (3) is 3 months post 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 is using an effective contraceptive method including intrauterine device, hormonal contraceptives (i.e., vaginal ring, implant, oral, injectable or patch) for at least 30 days before baseline, and agrees to continue using the contraceptive method through at least 10 days after the completion of study therapy. Vasectomy in the male partner is also an acceptable contraceptive method as long as performed at least 3 months prior to Baseline.

c. Subject is a female subject who is of reproductive potential and agrees to remain abstinent or use (or have her partner use) an acceptable barrier contraceptive methods from the time of consent through 10 days after the completion of study therapy. Acceptable barrier methods of contraception for this study are: male condom, female condom and diaphragm.

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

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

5. 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. For subjects under the legal age of consent, the subject's parent or legal representative must also be willing to sign the subject's ICF. Local regulations should be followed for consenting subjects under the age of consent.
6. Subject and/or parent/legal representative is able to understand and sign a consent or authorization form, which shall permit the use, disclosure and transfer of the subject's personal health information (e.g., in the US Health Information Portability and Accountability Act Authorization form).
7. Subject and/or parent/legal representative 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 <u>any</u> 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 vaginalis, Herpes* virus, *Neisseria gonorrhoeae, Chlamydia trachomatis*, symptomatic human papillomavirus or other mixed infections.
2. Subject received systemic and/or topical (vaginal) antifungal treatment, including prescription or over-the-counter products, within 28 days of the Baseline visit.

3. Subject has active menstruation at the Baseline visit.
4. Subject has uncontrolled diabetes mellitus.
5. Subject has a history of or an active cervical/vaginal cancer.
6. 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. Select strong CYP3A4/5 inhibitors and CYP3A4/5 inducers during the 7 days prior to enrollment and during study treatment until the TOC visit
    c. Select P-gp substrates during the 48 hours prior to enrollment or during study treatment.
7. Subject has a known hypersensitivity to 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 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.
11. Subject has received prior treatment with ibrexafungerp in a previous trial.
12. 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.
13. Subject is an employee of SCYNEXIS, Inc., the investigator or the contract research organization (CRO) involved in the study, or is an immediate family member (partner, offspring, parent, sibling, or sibling's offspring) of an employee involved in the study.
14. Subject is unlikely to comply with protocol requirements.

11.3 Discontinuation Criteria

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

- Withdrawal of consent by the subject and/or parent or legal representative;
- 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.

11.4 Early Termination

With effective oral therapy, immediate relief of all symptoms is not expected and subjects should not expect immediate relief.

If the subject experiences persistence or worsening or recurrence of symptoms that per the investigator's assessment (e.g., symptoms ≥3) warrant the use of rescue antifungal therapy, a vaginal examination with investigator's rating of signs should be completed. Additionally, vulvovaginal samples should be obtained for KOH testing and pH measurements by the local laboratory, fungal culture by the central laboratory and investigation of other pathogens such as bacterial vaginosis and *Trichomonas vaginalis* by the local laboratory.

If the KOH test is negative, the investigator should consider other causes for the persistence or worsening of the symptoms as antifungal rescue medication may not be indicated.

If the investigator's rating of the vulvovaginal signs and vaginal sample collection is not possible prior to the initiation of the rescue therapy, it should still be completed as soon as possible after rescue therapy is initiated.

In addition to the vaginal examination, the symptoms that led to the use of rescue antifungal therapy should be documented in the eCRF and the following procedures should also be completed:

- If rescue therapy is administered prior to or at the TOC visit, all TOC visit procedures should be completed and no additional visits will be needed. The subject will be considered as early termination due to lack of efficacy prior to or at TOC.
- If rescue therapy is administered after the TOC visit but prior to or at the FU visit, all FU visit procedures should be completed and no additional visits will be needed. The subject will be considered as early termination due to lack of efficacy after TOC but prior to or at FU.

Oral fluconazole [one 150-mg dose] may be provided to study sites as rescue medication. However, at the investigator's discretion other approved antifungal agent may be administered as rescue medication to a particular patient for whom fluconazole is not considered the optimal option. All rescue antifungal medications should be documented in the eCRF.

Details of study treatment groups and dietary requirements for treatment administration are provided in Section 12.1 and Section 12.2, respectively.

11.5 Replacement of Dropouts

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

12.0 Study Treatments

12.1 Study Treatment Groups

Subjects who meet all of the inclusion and none of the exclusion criteria will be enrolled into the study and will be randomized in a 2:1 ratio to either oral ibrexafungerp or ibrexafungerp matching placebo, as follows:

- Oral ibrexafungerp 300-mg dose BID for 1 day
- Oral ibrexafungerp matching placebo BID for 1 day

For the purpose of maintaining treatment blinding, all subjects randomized to placebo will receive matching ibrexafungerp placebo tablets. Subjects will receive their first dose of study drug at the site and will be dispensed the second dose for self-administration at home 12 hours after the first dose. The second study drug dose will be self-administered by the subjects approximately 12 hours later at home on Baseline (Day 1). If administering the first dose at the study center would complicate the administration of the subsequent dose, the subject can self-administer both doses at home to allow for a more convenient dosing schedule.

12.2 Dietary Requirements

There are no dietary requirements or restrictions for the administration of the study drug. It is recommended that study drug be administered preferably with food and with approximately 8 oz./240 mL of water.

12.3 Study Drugs

Study drug will consist of ibrexafungerp (150-mg tablets) and ibrexafungerp matching placebo tablets. Study drug will be provided by the Sponsor.

12.3.1 Ibrexafungerp (SCY-078) Description

Study Drug Identifier:	Ibrexafungerp
Empirical Formula:	$C_{50}H_{75}N_5O_{11}$ (citrate salt)
Molecular Weight:	922.18 (citrate salt)
Physical Description:	White to off-white solid

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

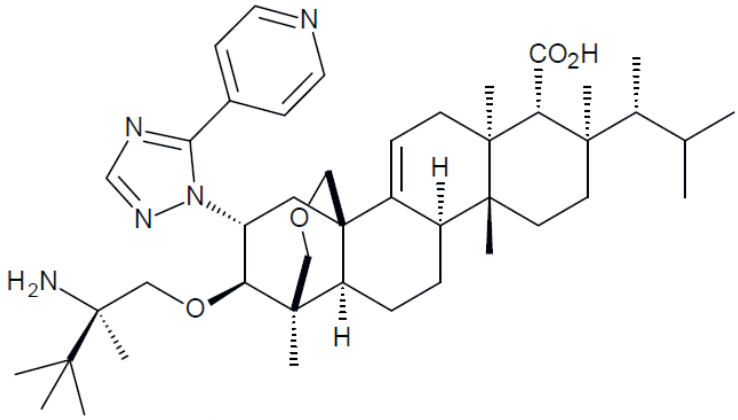

Figure 2 Chemical Structure of Ibrexafungerp Citrate (formerly SCY-078)

12.3.2 Formulation, Packaging and Labelling

Ibrexafungerp citrate drug product for oral administration will be supplied as a tablet containing 150 mg of ibrexafungerp 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.

The placebo product matching ibrexafungerp will be supplied as a tablet matching the size and appearance of the active tablet. The tablet formulation contains silicified microcrystalline cellulose, crospovidone, mannitol, colloidal silicon dioxide, magnesium stearate (non-bovine) and butylated hydroxyanisole.

The ibrexafungerp and matching placebo drug supplies will be packaged in bottles.

Bottles will contain 4 tablets of ibrexafungerp or matching placebo.

For the purpose of blinding, the number and appearance of dosage units will be the same across both treatment groups.

Labels on the bottles containing double-blind study medication information will any other information required by applicable regulations and may include the following information:

- Product name (Ibrexafungerp 150mg Tablet (Active or Placebo))

- Sponsor Name
- Study Protocol Number
- Place to write the subject number
- Study drug kit number
- Number of tablets per bottle
- Dosing instructions
- Storage conditions (e.g. room temperature 15°C – 30°C or 15°C – 25°C for EU)
- 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 Interactive Response System (voice or web-based) 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 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 remaining at the TOC visit (Day 8 - Day 14).
- Review subject diary and tablet 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

Subjects will be instructed to bring the assigned bottles of study medication (including empty bottles) with them to the TOC visit (Day 8 – Day 14) to assess treatment compliance. 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 30 days before Baseline (Day 1) through the TOC visit (Day 8 - Day 14) will be recorded on the subject´s diary and in the eCRF. Only the use of antifungal medications, vaginal (topical) medications, antibiotics for any reason or any other 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 will be recorded in the eCRF. Prior and concomitant medications will be reviewed and recorded at all scheduled and unscheduled study visits.

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
- Topical (vaginal) contraceptives
- Other investigational drug(s)
- Select strong CYP3A4/5 inhibitors, CYP3A4/5 inducers 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:

- CYP3A4 substrates, including but not limited to sirolimus, tacrolimus warfarin, cyclosporine and amiodarone
- 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 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 1.

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). For subjects under the legal age of consent, the subject's parent or legal representative will also sign the subject's ICF. Local regulations should be followed for consenting subjects under the age of consent.

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 site number followed by a 2-digit sequentially assigned subject number starting at 01, at each site. 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 study drug kit 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, at the TOC visit and at any unscheduled visit, if needed.

14.6 Urine Pregnancy Test

A urine pregnancy test based on the measurement of human chorionic gonadotropin with a sensitivity of at least 25 international units per liter 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. Samples for safety laboratory tests will be collected at the Screening and the TOC visits and at any unscheduled visit, 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 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 8-Day 14) and at the FU visit (Day 25 [(± 4]). Subjects will also assess their symptom at unscheduled visits, as needed.

If the subject experiences persistence or worsening or recurrence of symptoms that per the investigator's assessment (e.g. symptoms ≥3) warrant the use of rescue antifungal therapy, the rating of the symptoms that led to the use of rescue antifungal therapy must be documented in the eCRF and a vaginal examination with rating of signs by the investigator should be completed. If the investigator's rating of the vulvovaginal signs and vaginal samples collection are not possible prior to the initiation of the rescue therapy, they should still be completed as soon as possible after rescue therapy is initiated.

Subjects will rate their symptoms of infection using the VSS Scale, 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

Subjects will rate their symptoms and record their scores on the VSS Scale included in their subject diaries.

14.9 Vulvovaginal Samples for Identification of Other Pathogens and Vaginal pH

A vulvovaginal specimen will be obtained at the Screening visit for local vaginal pH determination. This sample will also be tested by a local qualified laboratory to rule out bacterial vaginosis and *Trichomonas vaginalis*. Testing for *Neisseria gonorrhoeae*, *Chlamydia trachomatis*

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, *T. vaginalis, N. gonorrhoeae*, *C. trachomatis* or *Herpes* virus at unscheduled visits only if needed. This procedure should also be completed prior to the initiation of rescue therapy. If the vaginal samples collection is not possible prior to the initiation of rescue therapy, it should still be completed as soon as possible after rescue therapy is initiated. If there is persistence or recurrence of vulvovaginal symptoms, additional vulvovaginal specimens will be collected at the TOC and at the FU visits.

Procedures for collecting and shipping vulvovaginal samples to the central laboratory will be described in the laboratory manual.

14.10 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 qualified designee. A vaginal sample will also be obtained at Screening and at the TOC visit for fungal culture and species identification by the central laboratory and for susceptibility testing against ibrexafungerp and additional antifungal agents (per CLSI M27-A3 guidelines). If there is persistence or recurrence of vulvovaginal symptoms, additional vulvovaginal specimens will be collected for KOH testing at the TOC and at the FU visits, and for fungal culture at the FU visit. Samples will also be obtained at any unscheduled visit, if needed.

If the subject experiences persistence or worsening or recurrence of symptoms that per the investigator's assessment (e.g. symptoms ≥3) warrant the use of rescue antifungal therapy, a vaginal examination with collection of samples for KOH (assess at the site) and culture should be completed prior to initiation of rescue therapy. If the KOH test is negative, the investigator should consider other causes for the persistence or worsening of the symptoms and antifungal rescue medication may not be indicated. If the collection of the vaginal culture is not possible prior to the initiation of the rescue therapy, it should still be collected as soon as possible after rescue therapy is given.

14.11 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 and TOC visits. The vulvovaginal examination will be repeated at the FU visit only if the subject presents symptoms. Otherwise, no additional vulvovaginal examination will be conducted or signs rated. Vulvovaginal examinations may be conducted at unscheduled visits, if needed.

If the subject experiences persistence or worsening or recurrence of symptoms that per the investigator's assessment (e.g. symptoms ≥3) warrant the use of rescue antifungal therapy, a

vaginal examination with rating of signs by the investigator should be completed prior to initiation of rescue therapy. If the investigator's rating of the vulvovaginal signs is not possible prior to the initiation of the rescue therapy, it should still be completed as soon as possible after rescue therapy is initiated.

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.

14.12 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 two study treatment groups. Subject randomization will be performed using an Interactive Response System (voice or web-based), 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), eligible subjects will be dispensed enough study medication to permit BID dosing of the assigned study medication (see Section 12.3.2) and a subject diary, where the subject will rate her vulvovaginal symptoms of infection and will record study drug dosing details, AEs and concomitant medication use daily from Day 1 through the TOC visit.

14.14 Study Drug Dosing

The first study drug dose will be preferably administered at the center and the second study drug dose will be self-administered by the subjects approximately 12 hours later at home on Baseline (Day 1). The 2 doses should be administered approximately 12 hours apart. If administering the first dose at the study center would complicate the administration of the second dose 12 hours later (e.g. first dose at 3 p.m. will require second dose at 3 a.m.), the subject can self-administer both doses at home to allow for a more convenient dosing schedule (e.g., 8 p.m. and 8 a.m.). Subjects will record study drug dosing details in their study diary.

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 study drug dosing details, 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 8-Day 14).

The site will 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 Study Drug Collection and Treatment Compliance Evaluation

Treatment compliance will be reviewed by the investigator or designee at the TOC (Day 8-Day 14) visit. Subjects will be instructed to bring all bottles (including empty bottles) of study medication with them to the visit to assess treatment 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.

The site will 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.

14.18 Vital Signs

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

14.19 Prior and Concomitant Medication Review

All medications (including prescription and over-the-counter medications, supplements, and herbal products) taken from 30 days before Baseline (Day 1) through the TOC visit (Day 8-Day 14) will be recorded on the subject's diary and eCRF. Only the use of antifungal medications, vaginal (topical) medications, antibiotics for any reason or any other 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 will be recorded in the eCRF. Prior and concomitant medications will be reviewed and recorded at all scheduled and unscheduled study visits.

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

14.20 Adverse Event Monitoring

AEs will be recorded and reviewed at all scheduled and unscheduled study visits from the time the ICF is signed. Subjects will record any AE in their study diary from Baseline (Day 1) through the TOC visit (Day 8-Day 14). 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 1).

Table 1: Schedule of Visits and Procedures (Study SCY-078-303)

Visit	V1 Screening[a]	V2 Baseline[a]	V3 TOC	V4 Follow-up	Unscheduled Visits
Day (allowable window)	**D-1 (-2)**	**D1**	**D11 (±3)**	**D25 (± 4)**	
Study Procedures					
Informed consent[b]	X				
Assignment of Subject ID number	X				
Inclusion/exclusion criteria	X	X			
Medical history and demographics	X				
Abbreviated physical exam	X		X		If needed
Urine pregnancy test[c]	X				If needed
Safety labs[d]	X		X		If needed
Rating of vulvovaginal symptoms by the subject[e]	X	X---------- X		X	If needed
Vulvovaginal sample for other pathogens and pH[e]	X		If symptoms	If symptoms	If needed
Vulvovaginal sample for KOH[e]	X		If symptoms	If symptoms	If needed
Vulvovaginal sample for fungal culture[e]	X		X	If symptoms	If needed

Visit	V1 Screening[a]	V2 Baseline[a]	V3 TOC	V4 Follow-up	Unscheduled Visits
Day (allowable window)	**D-1 (-2)**	**D1**	**D11 (±3)**	**D25 (± 4)**	
Study Procedures					
Rating of vulvovaginal signs by the investigator [e]	X		X	If symptoms[f]	If needed
Randomization		X			
Study drug and subject diary[g] dispensing		X			
Study drug dosing[h]		X			
Subject diary completion		X----------X			
Study drug collection and treatment compliance evaluation			X		
Subject diary collection and review			X		
Vital Signs	X		X		If needed
Prior & concomitant medication review	X	X	X	X	X
AE monitoring	X	X	X	X	X

Abbreviations: AE=adverse event; D=day; TOC=test of cure; V=visit

a. Screening and Baseline may occur on the same day.
b. For subjects under the legal age of consent, the subject's parent or legal representative will also sign the subject's ICF.
c. Results should be reviewed prior to randomization at Baseline (Day 1).
d. Hematology and blood chemistry. Safety laboratory tests will be performed by a qualified central laboratory.
e. If the subject experiences persistence or worsening or recurrence of symptoms, after the baseline visit, that per the investigator's assessment (e.g. symptoms ≥3) warrant the use of rescue antifungal therapy, the symptoms that led to the use of rescue antifungal therapy must be documented in the eCRF and a vaginal examination with rating of signs by the investigator should be completed. Additionally, vulvovaginal samples should be obtained for KOH testing

and pH measurement (both at the site), fungal culture (central laboratory) and investigation of other pathogens such as bacterial vaginosis and *Trichomonas vaginalis* (at the site). If the investigator's rating of the vulvovaginal signs and vaginal samples collection are not possible prior to the initiation of the rescue therapy, they should still be completed as soon as possible after rescue therapy is initiated.

f. Vulvovaginal examinations will be repeated at the FU visit only if the subject presents symptoms. Otherwise, no additional vulvovaginal examination will be conducted or signs rated.

g. Subject diaries will be used to rate vulvovaginal symptoms of infection and record study drug dosing details, AEs and concomitant medication use.

h. If administering the first dose at the study center would complicate the administration of the second dose 12 hours later (e.g. first dose at 3 p.m. will require second dose at 3 a.m.), the subject can self-administer both doses at home to allow for a more convenient dosing schedule (e.g., 8 p.m. and 8 a.m.). Subjects will record study drug dosing details in their study diary

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** total bilirubin >2 x ULN 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. Considering the dosing schedule in this study, one dose administered at the site and one dose administered at home approximately 12 hours later, overdose is not expected. If accidently the 2 doses of study drug are administered together, this should be recorded in the dosing section of the eCRF but will not require additional reporting unless associated with a SAE. An overdose must be reported within 24 hours of the site becoming aware of the overdose if such overdose occurs with an associated SAE.

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 the Safety Surveillance team 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.

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

The clinical cure and mycological eradication rates will be described by baseline *Candida* species, when the number of isolates per species allows.

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

The primary endpoint of the study is the percentage of subjects achieving a clinical cure at the TOC visit. Assuming clinical cure rates of 50% and 30% for ibrexafungerp and placebo administered in a 2:1 ratio, respectively, approximately 282 subjects will provide 90% power to detect a difference between ibrexafungerp and placebo based on a Pearson's Chi-squared test with a Type 1 error rate of 5%. Because it is expected that approximately 20% of subjects may not have a mycological culture-confirmed infection at Baseline and approximately 10% may withdraw early from the study, an additional 84 subjects are added for a total of 366 subjects (244 subjects randomized to ibrexafungerp and 122 subjects, to placebo).

18.2 Analysis Populations

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

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

Modified Intent-to-Treat (mITT) Population: All randomized subjects who have a positive culture for *Candida* species at Baseline.

Per-Protocol (PP) Population: All mITT subjects who have completed the study drug treatment AND who have a TOC evaluation.

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 (Day 8-Day 14) 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 Efficacy

18.6.1 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 culture for growth of *Candida* species) at the TOC visit, the percentage of subjects with clinical cure and mycological eradication at the TOC visit, the percentage of subjects with complete resolution of symptoms at the FU visit, and the percentage of subjects with clinical improvement (partial or complete resolution of signs and symptoms with a total composite score no greater than 1) at the TOC visit and the absolute change in signs and symptoms score from Baseline to TOC and FU visits.

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

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.

Mycological Outcome

- Mycological eradication: A subject with negative culture for *Candida* species.
- Mycological persistence: A subject with a positive culture for *Candida* species.

18.6.2 Efficacy Analyses

The efficacy analyses will be conducted using the mITT (primary analysis population), ITT and PP populations to evaluate ibrexafungerp vs. placebo.

The primary endpoint, percentage of subjects with clinical cure at TOC, will be analyzed using a Cochran Mantel Haenszel (CMH) test adjusted for site; the p-value and 95% confidence intervals will be presented. Missing Day 8-Day 14 (TOC) data for the primary endpoint 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. All other data will be analyzed as is with no imputation.

For other continuous efficacy endpoints, a two-way analysis of variance (ANOVA) model will be used including effects for treatment and site; p-values and 95% confidence intervals will be presented. For other categorical endpoints, the CMH test adjusted for site will be performed, and p-values and 95% confidence intervals will be presented.

18.7 Safety

18.7.1 Safety Assessments

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

AEs will be recorded and reviewed at all scheduled and unscheduled study visits from the time the Informed Consent Form is signed. An abbreviated physical examination, including general appearance and an overall examination of body systems, will be conducted at Screening and at the TOC visit. Vital signs, including blood pressure (systolic and diastolic), heart rate, respiratory rate and body temperature will be measured at the Screening and TOC visits, and at unscheduled visits, if needed. Safety laboratory tests

(hematology and blood chemistry) will be measured at Screening, at the TOC visit and at unscheduled visits, if needed. All prior and concomitant medications taken before Baseline (Day 1) through the TOC visit will be recorded. Only the use of antifungal medications, vaginal (topical) medications, antibiotics for any reason or any other medications to treat an AE will be recorded after the TOC visit through the last study visit (FU).

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

18.7.2 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. In the case of a minor, according to the local definition (e.g., below 16 or 18 years of age), a parent or legal representative should also sign and date the ICF. Local regulations should be followed for consenting subjects under the age of consent and original signed assent, when applicable, will be retained with the study center's records with the subject's ICF. 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 14.10) ,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. All samples will be identified only by a coded number to maintain subject confidentiality.

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. Diflucan prescribing information. Pfizer. Revised November 2014.
5. Sobel JD, Management of recurrent vulvovaginal candidiasis: unresolved issues. Curr Infect Dis Rep. 2006 Nov;8(6):481-6.
6. CLSI. 2008a. Reference method for broth dilution antifungal susceptibility testing of yeasts; approved standard – third edition. CLSI document M27-A3. Clinical and Laboratory Standards Institute, Wayne, PA.
7. 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 topical vaginal contraceptives is prohibited during the study. No systemic or topical vaginal antifungal treatment other than the study drug is allowed during the study unless used as rescue medication after the subject has been documented as not responding to study drug. No investigational drugs other than the study drug are allowed within 30 days before Screening and for the entire duration of the study. In addition, the medications listed below are also prohibited.

Strong CYP3A4/5 inhibitors and CYP3A4/5 inducers

CYP	Strong Inhibitors[a]		Inducers[a]
3A4/5	• boceprevir • clarithromycin • conivaptan • indinavir • lopinavir • mibefradil	• nefazodone • nelfinavir • ritonavir • saquinavir • telaprevir • telithromycin	• avasimibe • carbamazepine • phenytoin • rifampin • St. John's wort • long-lasting barbiturates

a. The CYP3A4/5 inhibitors and CYP3A4/5 inducers listed in this table are not permitted during the 7 days prior to enrollment and during study treatment until TOC.

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

CYP3A4 substrates

CYP	Substrates
3A4	*In vitro*, ibrexafungerp (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 ibrexafungerp (SCY-078) with drugs known to be CYP3A sensitive substrates with narrow therapeutic index, such as midazolam and cyclosporine. Subjects receiving sirolimus, tacrolimus, warfarin, cyclosporine or amiodarone are permitted for enrollment in the study and these medications may be administered concomitantly with ibrexafungerp (SCY-078) with close monitoring. Dosing adjustments and subsequent monitoring of sirolimus and warfarin should be undertaken in accordance with product prescribing information for the respective agents.

OATP1B3 substrates

OATP	Substrate
1B3	*In vitro*, ibrexafungerp (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 ibrexafungerp (SCY-078) with drugs known to be OATP1B3 selective substrates. Therefore, caution should be exercised when administering ibrexafungerp (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