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) Compared to Placebo in Subjects with Recurrent Vulvovaginal Candidiasis

SCYNEXIS Protocol Number SCY-078-304

SCYNEXIS, Inc.
1 Evertrust Plaza, 13th Floor
Jersey City, NJ 07302

Original Protocol Issue Date: 03 June 2019 (Version 1.0)

US IND Number 107,521

EudraCT Number: 2019-002600-40

1.0 Contact Information

Contract Research Organization	PPD
Study Medical Monitor	Nkechi Azie, MD
Clinical Project Manager	Philip Deane
Sponsor	SCYNEXIS, Inc. 1 Evertrust Plaza, 13th Floor Jersey City, NJ 07302 Phone: +1.201.884.5485 Fax: +1.201.884.5490 Email: info@scynexis.com

2.0 Protocol Approvals

PROTOCOL ID: SCY-078-304

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

SCYNEXIS, Inc. Approval:

David Angulo Chief Medical Officer 1 Evertrust Plaza, 13th Floor Jersey City, NJ 07302 Phone: 1 201 884 5471 E-mail: davidangulo@scynexis.com	Date

Investigator Agreement Statement`
PROTOCOL ID: SCY-078-304

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Oral Ibrexafungerp (SCY-078) Compared to Placebo in Subjects with Recurrent 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 subject. All patients will provide a written informed consent prior to participation.
I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I have read, understood and agree to abide by all the conditions and instructions contained in this protocol, and in compliance with International Conference on Harmonization (ICH) guidelines, Good Clinical Practices (GCP), Safety Reporting obligations and any applicable local requirements.

Principal Investigator's Signature	Date

Principal Investigator's Name (Printed)

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

3.0 Revision History

Not applicable

4.0 Abbreviations

ABBREVIATION	DEFINITION
AE	adverse event
ALT/SGOT	alanine aminotransferase
ANOVA	analysis of variance
AST/SGPT	aspartate aminotransferase
BID	twice a day
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
C_{max}	maximum concentration
CMH test	Cochran-Mantel-Haenszel test
CPK	creatine phosphokinase
CRO	contract research organization
CYP	cytochrome P450
EC	ethics committee
ECI	event of clinical interest
eCRF	electronic case report from
EDC	electronic data capture
EOFU	end of follow-up
FDA	Food and Drug Administration
FU	follow-up
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
hCG	human chorionic gonadotropin
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ID	identification

ABBREVIATION	DEFINITION
IRB	institutional review board
ITT population	intent-to-treat population
IWRS	Interactive web response
IV	intravenous
KOH	potassium hydroxide
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat population
OATP1B3	organic anion-transporting polypeptide 1B3
P-gp	P-glycoprotein
PI	principal investigator
PP population	per-protocol population
QD	once a day
QOL	quality of life
RBC	red blood cell
RVVC	recurrent vulvovaginal candidiasis
SAE	serious adverse event
SAP	statistical analysis plan
TOC	test of cure
ULN	upper limit of normal
VSS Scale	Vulvovaginal Signs and Symptoms Scale
VVC	vulvovaginal candidiasis
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) Compared to Placebo in Subjects with Recurrent Vulvovaginal Candidiasis

STUDY OBJECTIVES:

Primary Objective:

- To evaluate the efficacy of oral ibrexafungerp versus placebo in preventing recurrences of vulvovaginal candidiasis (VVC) in subjects with recurrent VVC (RVVC) based on Clinical Success.

Key Secondary Objective:

- To evaluate the efficacy of oral ibrexafungerp versus placebo in preventing recurrences of VVC in subjects with RVVC based on Mycologically Proven Recurrences at Test of Cure (TOC).

Other Secondary Objectives:

- To evaluate the efficacy of oral ibrexafungerp versus placebo in preventing recurrences (Mycologically Proven, Presumed or Suspected) of VVC in subjects with RVVC.
- To evaluate the efficacy of oral ibrexafungerp versus placebo in preventing recurrences of VVC in subjects with RVVC based on the number of Recurrences (Mycologically Proven, Presumed or Suspected) of VVC.
- To evaluate the efficacy of oral ibrexafungerp versus placebo in subjects with RVVC based on Quality of Life (QOL) outcomes.
- To evaluate the safety and tolerability of oral ibrexafungerp in subjects with RVVC.

STUDY ENDPOINTS:

Primary Endpoint:

- Efficacy as measured by the percentage of subjects with documented Clinical Success (defined as subjects having a TOC evaluation and no Mycologically Proven, Presumed or Suspected Recurrences of VVC) up to TOC (Week 24).

Key Secondary Endpoint:

- Efficacy as measured by the percentage of subjects with no Mycologically Proven Recurrence (defined as an episode of VVC with a total composite score ≥ 3 on the Vulvovaginal Signs and Symptoms [VSS] Scale and a culture positive for *Candida* spp. that required antifungal treatment) at TOC (Week 24).

Other Secondary Endpoints:

Efficacy as measured by:

- The percentage of subjects with no Mycologically Proven Recurrence at Week 4, Week 8, Week 12, and Week 36 (end of follow-up [EOFU]).

- The time to the first Recurrence (Mycologically Proven, Presumed or Suspected) of VVC through EOFU.
- The percentage of subjects with Mycological Eradication (negative fungal culture) at Week 12, Week 24 (TOC) and Week 36 (EOFU).
- The percentage of subjects with no Mycologically Proven, Presumed or Suspected Recurrences at Week 4, Week 8, Week 12 and Week 36 (EOFU).
- The percentage of subjects with no Mycologically Proven or Presumed Recurrences at Week 4, Week 8, Week 12, TOC (Week 24) and Week 36 (EOFU).
- The proportion of subjects in three ordered categories related to the number of Recurrences (Mycologically Proven, Presumed or Suspected) of VVC from Baseline (Day 1) to TOC (Week 24) and Week 36 (EOFU). The three categories of recurrence are defined as (i) 0 to 1 episodes, (ii) 2 to 3 episodes, and (iii) ≥ 4 episodes.
- The absolute number of Mycologically Proven, Presumed or Suspected Recurrences from Baseline (Day 1) to TOC (Week 24) and Week 36 (EOFU).
- Absolute improvement in QOL outcomes at Week 12, Week 24 (TOC) and Week 36 (EOFU) as measured by EQ-5D, SF-36 and FSDS.

Safety and tolerability as measured by:

- Adverse events (AEs), vital signs, treatment discontinuation and safety laboratory tests at TOC (Week 24).

STUDY PHASE: 3

STUDY DESIGN: This study is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of oral ibrexafungerp (formerly "SCY-078") compared to placebo in female subjects 12 years and older with RVVC. The primary objective of the study is to evaluate the efficacy of oral ibrexafungerp versus placebo in preventing recurrences of VVC in subjects with RVVC based on Clinical Success.

The study will consist of a Screening visit, an Acute Phase with open-label fluconazole and a Prevention of Recurrence Phase with randomized ibrexafungerp or placebo. Screening and the beginning of the Acute Phase (Day -14) may occur on the same day. Approximately 320 subjects are planned to be enrolled into the open-label Acute Phase of the study in order to randomize approximately 240 subjects into the double-blind Prevention of Recurrence Phase, which will consist of 6 monthly, single-day treatments with the randomized study drug.

A Nested Sub-Study will be made available to subjects who fail treatment with fluconazole during the Acute Phase and are not eligible for randomization into the Prevention of Recurrence Phase (see Section 21.3 [Appendix C] for Sub-Study details).

Study Visits

Study visits will consist of scheduled on-site visits, phone contacts, and lab visits (Acute Phase only), as well as unscheduled visits. Whenever possible, on-site visits and phone contacts will be scheduled to occur on the date of dosing (or as close to the date of dosing as possible) to facilitate reminding subjects to take their study doses. This is applicable for the Baseline (Day 1), Week 4, Week 8, Week 12, Week 16 (phone contact), and Week 20 (phone contact) visits.

Phone contacts will be conducted to check for AEs, treatment compliance, potential recurrence, and concomitant medication use, including other antifungal agents. Unscheduled visits will be conducted anytime that there are symptoms indicating a potential recurrence or an AE.

- **Screening (Days -16 to -14)**: To be eligible for inclusion, subjects must have a history of at least three episodes of VVC in the past 12 months (including the current episode), a total composite score ≥ 4 on the VSS Scale, a positive potassium hydroxide (KOH) test, and a normal vaginal pH (≤ 4.5). Screening and the beginning of the Acute Phase (Day -14) may occur on the same day.
- **Acute Phase (Days -14 to -1)**: Eligible subjects will receive active treatment with open-label oral fluconazole 150 mg administered once a day (QD) on Days -14, -11 and -8, for a total of 3 doses. Subjects will be dispensed subject diaries where they will rate their vulvovaginal symptoms.
- **Prevention of Recurrence Phase:** The occurrence of a recurrence is the key efficacy parameter in this study. Subjects who have a culture-confirmed *Candida* spp. infection from the sample collected at Screening, achieve significant resolution of their vulvovaginal signs and symptoms on fluconazole (defined as a total composite score ≤ 2 on the VSS Scale) at Baseline (Day 1) and continue to meet all other eligibility criteria will be randomized into the Prevention of Recurrence Phase. A Nested Sub-Study will be made available to subjects who fail treatment with fluconazole during the Acute Phase and are not eligible for randomization into the Prevention of Recurrence Phase. Subjects who are not eligible for this study or the Nested Sub-Study will be discontinued. Subjects will be assessed for potential recurrences throughout the Study Treatment Period and the Follow-up Period.

    - **Study Treatment Period (Baseline [Day 1] through Week 24 [TOC]):** Subjects will be randomized at a 1:1 ratio to receive one of two study treatments (oral ibrexafungerp or placebo administered as a single-day treatment repeated every 4 weeks [28 days (±3)] for a total of 6 single-day treatments) in a double-blind manner. Each single-day treatment will consist of two doses of ibrexafungerp 300 mg each or placebo given 12 (±4) hours apart (total single-day ibrexafungerp dose = 600 mg). Subjects will take the study drug on Day 1 (Baseline), Week 4, Week 8, Week 12, Week 16 and Week 20, regardless of recurrence or administration of antifungal medication. Subjects will receive their first dose of study drug at the site and self-administer the remaining doses at home. During the Study Treatment Period, both clinical and mycological evaluations will be completed at protocol-specified time points and anytime that there is suspicion of a potential recurrence. Vaginal examinations will be performed by the investigator to rate the signs of infection on the VSS Scale and subjects will rate their vulvovaginal symptoms on subject diaries on a weekly basis and at the time of each scheduled or unscheduled visit to the site. Mycological examinations will include KOH, fungal culture, species identification and susceptibility testing.
    - **Follow-up Period (Week 25 through Week 36 [EOFU]):** Subjects will enter the Follow-up Period regardless of recurrence or rescue antifungal medication use. Both clinical and mycological evaluations will be completed at protocol-specified time points during the Follow-up Period, and anytime that a recurrence is presumed. Subjects will complete all follow-up (FU) visits regardless of recurrence or rescue antifungal medication use and rate their vulvovaginal symptoms in their subject diaries on a weekly basis until the EOFU (Week 36 visit). Subjects will continue to be evaluated for potential recurrence, antifungal medication use and safety throughout this period.

Recurrences during the Prevention of Recurrence Phase

The occurrence of a recurrence is the key efficacy parameter in this study. Randomized subjects will be assessed for potential recurrence at all visits during the Prevention of

Recurrence Phase following Day 1 (Baseline) (i.e., from Day 2 through Week 36 [EOFU]), including phone contacts, scheduled visits and unscheduled visits, as well as in between visits. If during a phone contact or at any other time there is suspicion of a potential recurrence (any kind of recurrence, i.e., Mycologically Proven, Presumed or Suspected), subjects will be instructed to visit the study center for a proper evaluation of their recurrence before initiating any VVC treatment.

Potential recurrences will be assessed based on clinical and mycological outcomes and need for other antifungal treatment**.** If a subject has symptoms suggestive of *Candida* infection (itching, burning, irritation) that in the opinion of the investigator may require antifungal therapy, the following procedures must be completed:

- Rate and document symptoms in the electronic case report form (eCRF),
- Perform vaginal examination to rate signs and document in the eCRF,
- Measure vaginal pH at the site and document results in the eCRF,
- Collect vaginal sample for KOH testing and investigation of potential bacterial vaginosis and *Trichomonas vaginalis* infection at the site or by the local laboratory, and
- Collect vaginal samples for fungal culture by the central laboratory.

All of the procedures above should be completed prior to administration of rescue antifungal medication. **Subjects participating in the study should be strongly discouraged from self-administering any treatment for a potential recurrence**. Ideally, if the severity of the symptoms allows based on the investigator's judgment, the initiation of antifungal therapy should be delayed until results from the vaginal culture are available to confirm that the episode is due to *Candida* spp. and not to other cause of vaginitis.

In this study, Recurrences of VVC will be broken into three categories:

- **Mycologically Proven Recurrence:** An episode of VVC with a total composite score ≥ 3 on the VSS Scale and a culture positive for *Candida* spp. that required antifungal treatment.
- **Presumed Recurrence:** An episode of VVC with a total composite score ≥ 3 on the VSS Scale that required antifungal treatment and for which there is a positive KOH microscopy but no positive fungal culture.
- **Suspected Recurrence**: An episode of VVC that required treatment with an antifungal agent (including self-administration with over-the-counter antifungals) regardless of VSS composite score but for which there is no mycological evidence of disease, such as a positive KOH microscopy or fungal culture.

Subjects with a **Mycologically Proven Recurrence** should receive antifungal therapy.

If a subject experiences one or more recurrences during the Study Treatment Period Phase (i.e., either a Mycologically Proven Recurrence or a Presumed Recurrence or a Suspected Recurrence) she will continue her scheduled study drug administration and will complete all scheduled visits until reaching EOFU.

All antifungal therapy administered during the study should be documented in the electronic data capture (EDC) system, with the reason for use clearly indicated (e.g., Mycologically Proven Recurrence, Presumed Recurrence, Suspected Recurrence).

Efficacy (Clinical, Mycological and Patient-Reported Outcomes [QOL]) and Safety Assessments

Efficacy assessments will be based on clinical evaluations, mycological testing and quality of life (QOL) questionnaires. The primary efficacy endpoint of the study is the percentage of subjects with documented Clinical Success (defined as subjects having a TOC evaluation and no Mycologically Proven, Presumed or Suspected Recurrences of VVC) up to TOC (Week 24). The key secondary efficacy endpoint is the percentage of subjects with no Mycologically Proven Recurrence (defined as an episode of VVC with a total composite score ≥ 3 on the VSS Scale and a culture positive for *Candida* spp. that required antifungal treatment) at TOC (Week 24). Efficacy will also be assessed by other secondary efficacy and patient-reported outcomes (see STUDY ENDPOINTS above).

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

Clinical Evaluation

The signs (edema, erythema and excoriation or fissures) and symptoms (itching, burning and irritation) of infection will be assessed by the investigator and the subject, respectively, on the VSS Scale. The VSS Scale is a standardized, pre-defined 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 VSS score. The symptoms of infection will be rated by the subject on a weekly basis and at the time of each scheduled or unscheduled visit to the site throughout the Prevention of Recurrence Phase. Vaginal examinations will be conducted by the investigator to rate the subject's signs of infection at protocol-specified visits and anytime that there is suspicion of a potential recurrence.

Mycological Testing

Mycological tests will include direct wet mount microscopic examination to visualize clue cells indicative of bacterial vaginosis or trichomonas, direct microscopic examination with 10% KOH to identify yeast, and fungal cultures. The direct wet mount and KOH examination will be performed locally at Screening for the determination of subject eligibility and then anytime that a recurrence is suspected. 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. Fungal cultures will be performed centrally at Screening and at protocol-specified time points for species identification and susceptibility testing. Fungal cultures will also be done anytime that a recurrence is suspected during the Prevention of Recurrence Phase and for antifungal susceptibility testing for subjects with positive cultures.

Quality of Life

QOL will be assessed by EQ-5D, SF-36 and FSDS at protocol-specified time points to assess improvement in QOL outcomes.

TARGET POPULATION: The study population will include female subjects 12 years and older with RVVC.

INCLUSION CRITERIA:

Subjects must fulfill all of the following **KEY** criteria at Screening and/or Baseline (Day 1) to be eligible for study admission:

1. Subject is a post menarchal female subject 12 years and older at Screening 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 prior to administration of the initial dose of study drug.

2. Subject has a diagnosis of symptomatic VVC that meets the following criteria at Screening:
   a) A total composite score of ≥ 4 on the VSS Scale.
   b) Positive microscopic examination with 10% KOH in a vaginal sample collected at Screening revealing yeast forms (hyphae/pseudohyphae) or budding yeasts
   c) Normal vaginal pH (≤ 4.5).
   d) A minimum of three episodes of VVC in the past 12 months, including the current episode, that required administration of antifungal medication. Besides the current episode, at least one of the previous episodes in the past 12 months is required to have been a physician-diagnosed episode of VVC, with at least one positive test confirming vaginal yeast infection (e.g., KOH, culture or fungal polymerase chain reaction).
3. Subject meets the following criteria at Baseline (Day 1):
   a) Significant resolution of signs and symptoms of *Candida* infection (total composite score ≤ 2 on the VSS Scale).
   b) Culture positive for *Candida* spp. in a vaginal sample collected at Screening.
   c) Normal vaginal pH (≤ 4.5).
4. Subject is able to take oral tablets and capsules.

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 RVVC 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*, *Herpes* virus, *Neisseria gonorrhoeae*, *Chlamydia*, symptomatic human papillomavirus infection or other mixed infections.
2. Subject received systemic and/or topical vaginal antifungal treatment, including prescription or over-the-counter products, within 28 days prior to the Day -14 visit.
3. Subject is receiving or anticipates to require treatment with the prohibited medications (including prescription and over-the-counter medications, supplements, and herbal products) during the following timeframes:
   a) Systemic and topical vaginal antifungal treatment other than study drug and rescue medication (if needed), as specified in the protocol, anytime during the study.
   b) Select CYP3A4/5 inducers during the 14 days prior to enrollment and during study treatment
   c) Select strong CYP3A4/5 inhibitors during 48 hours prior to enrollment and during study treatment.
   d) Select P-gp substrates during the 48 hours prior to enrollment or during study treatment with ibrexafungerp.
   e) Topical vaginal corticosteroids from 7 days prior to the Screening visit to the Week 24 (TOC) visit.
4. Subject has active menstruation at the Screening visit. **Note:** The Screening visit may be rescheduled if required.
5. Subject has a history of or an active cervical/vaginal cancer.

STUDY DRUGS:

The study drug administered during the study will consist of oral ibrexafungerp (150-mg tablets) and ibrexafungerp matching placebo tablets for the double-blind Prevention of

Recurrence Phase, and oral fluconazole (150-mg tablets or capsules) for the open-label Acute Phase. 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 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.

Fluconazole drug product will be sourced commercially and will be provided as a tablet or capsule containing 150 mg of active ingredient.

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.

STUDY TREATMENT GROUPS:

Acute Phase

Subjects who meet all study eligibility criteria at Screening will enter the Acute Phase of the study and will receive oral fluconazole, as follows:

- Oral fluconazole 150 mg QD on Days -14, -11 and -8

The first dose of fluconazole will be administered on Day -14 at the study site, after all other visit procedures have been done. Subjects will self-administer the remaining doses at home.

Prevention of Recurrence Phase

Subjects who have a culture-confirmed VVC from the sample collected at Screening, achieve a significant resolution of the signs and symptoms of infection (total composite score ≤ 2 on the VSS Scale) at Baseline (Day 1) and continue to meet all study eligibility criteria will be randomized at a 1:1 ratio to one of the following two treatment groups:

- Oral ibrexafungerp administered as a single-day treatment repeated every 4 weeks (28 days [±3]) for a total of 6 single-day treatments (Baseline [Day 1], Week 4, Week 8, Week 12, Week 16 and Week 20). Each single-day treatment will consist of two doses of 300 mg each given 12 (±4) hours apart (total single-day dose = 600 mg).
- Matching oral placebo administered as a single-day treatment repeated every 4 weeks (28 days [±3]) for a total of 6 single-day treatments (Baseline [Day 1], Week 4, Week 8, Week 12, Week 16 and Week 20). Each single-day treatment will consist of two doses of placebo given 12 (±4) hours apart.

Subjects will receive their first dose of double-blind study drug at the site and will self-administer the remaining doses at home. Subjects must take the two doses of study drug 12 hours apart (±4 hours), preferably with or immediately after a meal.

STUDY BLINDING, RANDOMIZATION AND STRATIFICATION: This is a randomized, double-blind study. All site and sponsor personnel will be blinded to treatment assignment.

Approximately 320 subjects are planned to be enrolled into the open-label Acute Phase of the study in order to randomize approximately 240 subjects at a 1:1 ratio to one of the two study treatment groups. All randomization of subjects will be managed electronically through an interactive web response system (IWRS).

Subjects will be stratified at randomization based on the presence or absence of uncontrolled diabetes mellitus, defined as A1C levels ≥ 8.00% at Baseline (Uncontrolled diabetes mellitus: YES or NO), and by geographical region (USA or Ex-USA).

STUDY EVALUATIONS

Clinical Evaluation: The signs (edema, erythema and excoriation or fissures) and symptoms (itching, burning and irritation) of infection will be assessed by the investigator and the subject, respectively, on the VSS Scale. 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 wet mount microscopic examination to visualize clue cells indicative of bacterial vaginosis or trichomonas, direct microscopic examination with 10% KOH to identify yeast, and fungal cultures.

QOL: QOL will be assessed by EQ-5D, SF-36 and FSDS at protocol-specified time points to assess improvement in QOL outcomes.

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

STATISTICAL ANALYSES:

Sample Size Determination

The primary endpoint of the study is the percentage of subjects with documented Clinical Success up to TOC (Week 24). Assuming response rates of 65% and 43% for ibrexafungerp and placebo, respectively; 90% power; and an alpha level of 0.05, approximately 240 subjects randomized at a 1:1 ratio are needed to declare a difference between ibrexafungerp and placebo at Week 24 based on Fisher's Exact test.

In order to be randomized, a subject should have achieved the proposed significant resolution of signs and symptoms (total composite score ≤2 on the VSS Scale) after receiving fluconazole therapy for an acute episode and have a positive culture for *Candida* spp. from the sample collected at Screening. It is estimated that approximately 320 subjects will need to enter the Acute Phase to provide 240 subjects randomized to the Prevention of Recurrence Phase. Enrollment into the Acute Phase will be discontinued when approximately 240 subjects have been randomized.

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 confirmed mycological culture for yeast at Screening and a negative culture for yeast at Baseline (Day 1).
- Per-Protocol (PP) Population: All ITT subjects who did not have major protocol deviations likely to affect study efficacy and who have available data at the TOC visit. Note that subjects who discontinue due to a study-drug-related AE will be classified as failures for the analyses of efficacy under the PP population.
- Safety Population: All randomized subjects who received at least one dose of study drug (ibrexafungerp or placebo) and who have at least one post-Baseline (Day 1) evaluation.

Efficacy Analysis

Efficacy assessments will be based on clinical evaluations, mycological testing and QOL.

The **primary efficacy endpoint** of the study is the percentage of subjects with documented Clinical Success (defined as subjects having a TOC evaluation and no Mycologically Proven, Presumed or Suspected Recurrences of VVC) up to TOC (Week 24). The **key secondary efficacy endpoint** is the percentage of subjects with no Mycologically Proven Recurrence (defined as an episode of VVC with a total composite score ≥ 3 on the VSS Scale and a culture positive for *Candida* spp. that required antifungal treatment) at TOC (Week 24). **Other secondary efficacy endpoints** will also be assessed (see STUDY ENDPOINTS above).

The following efficacy outcomes will be evaluated in the study:

- **Clinical Success**: Subjects having a TOC evaluation and no Mycologically Proven, Presumed or Suspected Recurrences of VVC.
- **Recurrence of VVC**: In this study, Recurrence of VVC will be broken into three categories:
    - **Mycologically Proven Recurrence:** An episode of VVC with a total composite score ≥ 3 on the VSS Scale and a culture positive for *Candida* spp. that required antifungal treatment.
    - **Presumed Recurrence:** An episode of VVC with a total composite score ≥ 3 on the VSS Scale that required antifungal treatment and for which there is a positive KOH microscopy but no positive fungal culture.
    - **Suspected Recurrence**: An episode of VVC that required treatment with an antifungal agent (including self-administration with over-the-counter antifungals) regardless of VSS composite score but for which there is no mycological evidence of disease, such as a positive KOH microscopy or fungal culture.
- **Mycological Eradication:** Negative fungal culture (no growth of *Candida* species).

The primary endpoint, the percentage of subjects with documented Clinical Success up to TOC (Week 24), will be analyzed using a Cochran-Mantel-Haenszel (CMH) test adjusted for site; p-values and 95% confidence intervals will be presented. Subjects whose results are missing at TOC (Week 24) will be imputed as failures in the analysis. In the event that model convergence is an issue with a stratified analysis, alternative methods for accounting for site, or an unstratified analysis will be considered. A sensitivity analysis will be performed on the ITT population where subjects with missing values will be removed from the analysis.

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.

For the ordered categorical endpoint, a proportional odds model will be fitted accounting for the effects of treatment and site. The proportional odds model will fit an ordered regression model for the ordinal dependent variable as described by McCullagh (1980). If the assumption of proportional odds is violated alternative analyses will be considered which require a weaker assumption.

Safety Analysis

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

medications.

No formal statistical analysis is planned for the safety data. 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 serious AEs (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.

Laboratory evaluations and vital signs will be summarized as observed values and as changes from Baseline (Day 1) by treatment group. In addition, shifts (with respect to the reference range) from Baseline (Day 1) will be presented for laboratory tests by treatment group.

6.0 Schematic of Study Design

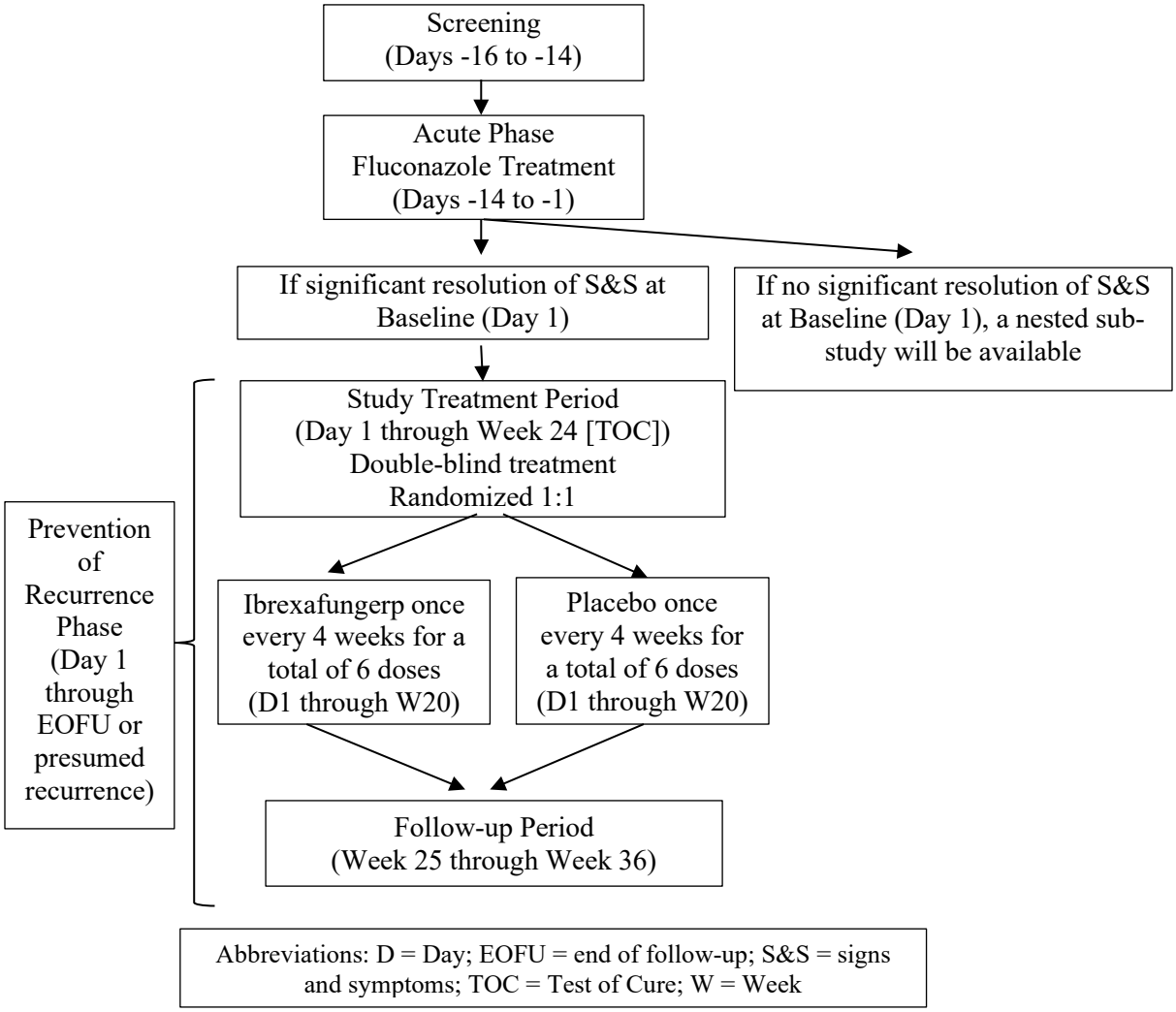


Figure 1 Schematic of Study Design

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 (RVVC).[3]

Current treatments for VVC include topical antifungals and the use of oral prescription antifungals, such as single doses of fluconazole. There are no currently approved products to prevent recurrence of VVC in patients with RVVC. The entity of RVVC has been defined as at least three symptomatic episodes in the previous 12 months, although some investigators define it as four attacks in a year. This is an entirely arbitrary differentiation, not based on any data or study and it is likely that women identified by both definitions are identical.[4]

C. albicans is responsible for the majority of infections in women with RVVC and the majority remain susceptible to azoles implying that the host, along with the pathogen, contributes to the pathophysiology of RVVC.

RVVC is likely a multifactorial disease including genetic predisposition to enhanced vaginal colonization where, in the presence of secondary triggering mechanisms, the carrier state is transformed into a proinflammatory state by a host's hyperactive local immune response. Long-term antifungal suppressive therapy may help control the host's mucosal reaction by keeping the vaginal fungal load at markedly reduced levels.[4] Several long-term maintenance regimens using either topical azoles or oral azoles (e.g., ketoconazole, itraconazole, and fluconazole) have been studied showing benefit in preventing recurrences of VVC. Although there have been few comparative studies, the best results were obtained with long-term maintenance therapy using once weekly fluconazole 150 mg for 6 months.[5,6] The most important limitation of the suppressive therapy with fluconazole is exactly that: suppression of growth rather than eradication of the yeast. Even though yeast organisms are dramatically reduced in number, below the level of detection by conventional culture technique, they persist in low numbers in the vaginal lumen, triggering the VVC episode upon discontinuation of fluconazole. A fungicidal drug and regimen may be able to address this significant limitation of current therapies for RVVC and may be associated with a more sustained benefit after discontinuation of therapy.

This study aims to demonstrate the efficacy and define the safety of a 6-month dosing regimen of oral ibrexafungerp to prevent recurrences in subjects with RVVC.

The glucan synthesis inhibitor ibrexafungerp

Ibrexafungerp (SCY-078) is a member of a new class of antifungal agents and is an orally active, semi-synthetic, triterpene derivative of the natural product enfumafungin. Ibrexafungerp is a

structurally distinct class of glucan synthesis inhibitor that inhibits the synthesis of the fungal cell wall polymer β-(1,3)-D-glucan. Time-kill studies have demonstrated that ibrexafungerp has *in vitro* fungicidal activity against *Candida* spp. isolates similar to that observed with the echinocandins.

Ibrexafungerp is being developed as the first oral and intravenous (IV) glucan synthesis inhibitor for the treatment and prevention of fungal infections caused by *Candida* and *Aspergillus* species with the potential to provide the therapeutic advantages of both an IV and oral formulation.

Antifungal activity

The spectrum and potency of activity of ibrexafungerp has been evaluated by numerous independent laboratories against an extensive panel of clinically relevant yeast and mold isolates using the Clinical and Laboratory Standards Institute (M27-A3 guidelines)[7] and European Committee on Antimicrobial Susceptibility Testing methods. Overall, the epidemiological studies have demonstrated that ibrexafungerp 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 for the treatment of invasive fungal infections.

Activity against *Candida* spp.

Ibrexafungerp has been evaluated against > 2000 *Candida* isolates, including all clinically relevant species, more than 300 *C. glabrata* isolates and 100 *C. auris* isolates. These *in vitro* studies have demonstrated the broad spectrum of anti-*Candida* activity of ibrexafungerp. Additionally, ibrexafungerp demonstrated *in vitro* activity against pre-formed biofilms, which is a relevant feature when addressing catheter-related *Candida* infections and, potentially, RVVC. Studies conducted with azole- and echinocandin-resistant strains have shown that ibrexafungerp retains activity (i.e., no significant change in minimum inhibitory concentration when compared to wild type) against > 90% of azole-resistant strains and > 70% of *Candida* strains with *FKS* mutations commonly associated with echinocandin resistance. Interestingly, although ibrexafungerp 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 was evaluated *in vitro* against clinical isolates of echinocandin-resistant strains of *Candida* spp., the majority of which contained mutations in the *FKS* gene. Overall, it was active against the majority of the echinocandin-resistant strains tested. Significantly, ibrexafungerp 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 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 did not select for mutations at positions S663 or S645. These results suggest that ibrexafungerp 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 was active against > 70% of these isolates. Ibrexafungerp has also demonstrated a potent activity against life-threatening and multi-drug-resistant *C. auris* strains at concentrations indicative of potential clinically relevant effects.

Activity against *Aspergillus* spp.

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

Murine models of invasive fungal infections

The antifungal efficacy of ibrexafungerp has been evaluated in several murine models of disseminated candidiasis and aspergillosis. In a disseminated *C. albicans* model, ibrexafungerp was more active than fluconazole at all doses. Murine models of ibrexafungerp in disseminated candidiasis caused by *C. glabrata* and *C. tropicalis* indicated activity across multiple *Candida* species. The ibrexafungerp area under the concentration-time curve 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 following oral administration for 6 and 9 months, respectively. The results from the non-clinical safety program are supportive of the doses and treatment duration intended in this study.

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

Clinical experience

To date, over 500 subjects and patients have received either oral or IV formulations of ibrexafungerp in Phase 1 and Phase 2 studies. Ibrexafungerp 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 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 or fluconazole. Ibrexafungerp was well tolerated, with an AE profile typical of this population, with the most common treatment-related AEs being gastrointestinal in nature (i.e., nausea and diarrhea). The results from this study also indicated that the higher dose of ibrexafungerp tested (750 mg once a day [QD]) is predicted to achieve the target exposure at steady state in the majority of patients.

A Phase 2 proof-of-concept study of oral ibrexafungerp in patients with acute VVC has also been completed. In this multicenter, randomized, active-controlled, evaluator-blinded study of oral ibrexafungerp compared to oral fluconazole in adult female patients with acute VVC, 96 patients with an acute, moderate to severe, symptomatic episode of vulvovaginal candidiasis were randomized at a 1:1:1 ratio to receive either oral ibrexafungerp 750 mg with a 1250 mg loading dose for three days, oral ibrexafungerp 750 mg with a 1250 mg loading dose for five days or a single dose of oral fluconazole. Ibrexafungerp 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 ibrexafungerp in this form of *Candida* infection.

In addition, a Phase 2 study to compare the safety and efficacy of oral ibrexafungerp vs. oral fluconazole in subjects with acute VVC (DOVE) has been completed. The primary objective of the study was dose selection for our Phase 3 pivotal program in VVC. This Phase 2b study was a randomized, multicenter, double-blind, active-controlled, dose-finding study designed to evaluate the safety, efficacy, tolerability and pharmacokinetics of five dosing regimens of oral ibrexafungerp in patients with moderate-to-severe (defined as a signs and symptoms score of 7 or greater) acute VVC, with oral fluconazole 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 dosing durations explored were 1 or 3 days. The maximum duration of treatment of 3 days was based on a previous Phase 2a study, 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 endpoints 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 signs and symptoms score of 0 or 1, the absolute change in signs and symptoms from Baseline and the need for rescue antifungal therapy.

All doses tested achieved meaningful clinical cure and mycological eradication rates but the dose that provides the best combination of attributes for this indication is the ibrexafungerp 600 mg dose administered as 300 mg twice a day (BID) for 1 day.

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

At Day 25, the follow-up (FU) visit, the ibrexafungerp 600 mg dose showed a trend towards improved clinical and mycological outcomes when compared to the fluconazole arm. If patients continued to have signs and symptoms of VVC at the TOC visit or later, rescue antifungal medication could be prescribed. Seven patients treated with fluconazole received rescue antifungal medication, whereas one patient treated with ibrexafungerp 600 mg received rescue antifungal medication. The rate of patients with no signs and symptoms (score = 0) at the FU visit was 70% for the ibrexafungerp 600 mg dose versus 50% for the fluconazole arm. A similar difference was observed when performing the analysis using a signs and symptoms score of 0 or 1, where this improvement was achieved by 81% of the subjects receiving ibrexafungerp 600 mg

dose versus 58% of the subjects receiving fluconazole. This demonstrates sustained symptom relief for at least 25 days and supports the monthly dosing proposed in this study

The oral ibrexafungerp 600 mg dose was generally well tolerated, with self-limiting (generally one-day duration), mild to moderate gastrointestinal AEs being the most commonly reported. Nausea was reported in three (10%) subjects in the ibrexafungerp 600 mg dose arm compared to two (6%) subjects in the fluconazole arm. Diarrhea and loose stool were reported in five (17%) subjects in the ibrexafungerp 600 mg dose arm compared to one (3%) subject in the fluconazole arm. Abdominal pain was reported in one (3%) subject in the ibrexafungerp 600 mg dose arm compared to 5 (16%) subjects in the fluconazole arm. No vomiting, severe AEs or discontinuations due to AEs were reported in the ibrexafungerp 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 exposure, while diltiazem (a moderate inhibitor of CYP3A) induces a mild to moderate (< 3-fold) increase in ibrexafungerp exposure. Ibrexafungerp did not have any effect on rosiglitazone (a CYP2C8 substrate) exposure, had only a mild effect (less than a 0.5-fold increase) on the area under the curve of tacrolimus (a CYP3A and P-glycoprotein [P-gp] substrate) and had no effect on the maximum concentration (C_{max}) of tacrolimus.

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

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

7.2 Rationale for the Study

RVVC is a major unmet medical need in women and there is currently no approved drug for the prevention of recurrences. This is a Phase 3 study of ibrexafungerp versus placebo being performed to evaluate the efficacy and safety of oral ibrexafungerp, a novel triterpenoid beta-glucan synthase inhibitor with broad spectrum antifungal activity and demonstrated sustained relief in acute VVC when given once a month for the prevention of RVVC in female subjects 12 years and older with RVVC.

A Nested Sub-Study will be available to a subgroup of subjects who fail fluconazole therapy in the Acute Phase. Details of the Nested Sub-Study are provided in Section 21.3 (Appendix C).

7.2.1 Rationale for Study Indication and Population

Considering the properties of ibrexafungerp as a potent antifungal compound with fungicidal activity against *Candida* spp., if ibrexafungerp is proven effective, it will represent an important treatment for subjects suffering from RVVC.

7.2.2 Rationale for Selected Dosing Regimen

Continued antifungal suppressive therapy is recommended for the treatment of RVVC. Previous studies have indicated that 6 months of continued suppressive azole therapy may be appropriate for the prevention of RVVC.[6]

In this study, oral ibrexafungerp will be administered as a single-day treatment repeated every 4 weeks (28 days [±3]) for a total of 6 single-day treatments. Each single-day treatment will consist of two doses of 300 mg each given 12 (±4) hours apart (total single-day dose = 600 mg). This dose level is the dose level used in the Phase 2b DOVE study in acute VVC, which was shown to be effective in achieving high clinical cure and mycological eradication rates. This dose level will be administered once every 4 weeks (28 days [±3]) for a total of 6 single-day treatments. The once-every-four-weeks dosing regimen was selected based on the fact that, in the DOVE study, the selected dose showed a sustained clinical benefit with high cure rates for up to 25 days (last follow-up).

7.2.3 Rationale for Study Endpoints and Efficacy Outcomes

In this study, recurrent VVC will be broken into three categories:

- **Mycologically Proven Recurrence:** An episode of VVC with a total composite score ≥ 3 on the VSS Scale and a culture positive for *Candida* spp. that required antifungal treatment.
- **Presumed Recurrence:** An episode of VVC with a total composite score ≥ 3 on the VSS Scale that required antifungal treatment and for which there is a positive KOH microscopy but no positive fungal culture.
- **Suspected Recurrence**: An episode of VVC that required treatment with an antifungal agent (including self-administration with over-the-counter antifungals) regardless of VSS composite score but for which there is no mycological evidence of disease, such as a positive potassium hydroxide (KOH) microscopy or fungal culture.

The primary endpoint of the study will be the percentage of subjects with documented Clinical Success (defined as subjects having a TOC evaluation and no Mycologically Proven, Presumed or Suspected Recurrence of VVC) up to TOC (Week 24). This criterion is meant to reflect real world practice, where patients may self-treat, and apply scientific rigor in assigning subjects with signs and symptoms of disease, regardless of culture result or missing data, as failures.

The key secondary endpoint will be the percentage of subjects with no Mycologically Proven Recurrence at TOC (Week 24). The key secondary endpoint is based on recurrences that are symptomatic and required antifungal therapy. This criterion is aimed at reflecting the highest level of certainty in the diagnosis of a recurrence in a symptomatic subject seeking medical treatment. This endpoint is anticipated to objectively demonstrate the antifungal activity of ibrexafungerp.

These endpoints are considered appropriate to identify the key clinical benefit intended with this preventive regimen.

7.2.4 Rationale for the Study Design

This Phase 3 trial is being conducted as a randomized, double-blind, placebo-controlled study. This design is deemed appropriate in consultation with regulatory agencies for this indication, considering that there are no approved therapies to prevent recurrences in subjects with RVVC.

It is expected that the data generated from this study, along with supportive data from studies of ibrexafungerp in acute VVC, will provide substantive evidence of the safety and efficacy of the proposed dosing regimen of ibrexafungerp to seek regulatory approval for the prevention of RVVC.

8.0 Study Objectives

8.1 Primary Objective

- To evaluate the efficacy of oral ibrexafungerp versus placebo in preventing recurrences of VVC in subjects with RVVC based on Clinical Success.

8.2 Key Secondary Objective

- To evaluate the efficacy of oral ibrexafungerp versus placebo in preventing recurrences of VVC in subjects with RVVC based on Mycologically Proven Recurrences at TOC.

8.3 Other Secondary Objectives

- To evaluate the efficacy of oral ibrexafungerp versus placebo in preventing recurrences (Mycologically Proven, Presumed or Suspected) of VVC in subjects with RVVC.
- To evaluate the efficacy of oral ibrexafungerp versus placebo in preventing recurrences of VVC in subjects with RVVC based on the number of Recurrences (Mycologically Proven, Presumed or Suspected) of VVC.
- To evaluate the efficacy of oral ibrexafungerp versus placebo in subjects with RVVC based on Quality-of-Life (QOL) outcomes.
- To evaluate the safety and tolerability of oral ibrexafungerp in subjects with RVVC.

9.0 Study Endpoints

9.1 Primary Endpoint

- Efficacy as measured by the percentage of subjects with documented Clinical Success (defined as subjects having a TOC evaluation and no Mycologically Proven, Presumed or Suspected Recurrence of VVC) up to TOC (Week 24).

9.2 Key Secondary Endpoint

- Efficacy as measured by the percentage of subjects with no Mycologically Proven Recurrence (defined as an episode of VVC with a total composite score ≥ 3 on the VSS Scale and a culture positive for *Candida* spp. that required antifungal treatment) at TOC (Week 24).

9.3 Other Secondary Endpoints

Efficacy as measured by:

- The percentage of subjects with no Mycologically Proven Recurrence at Week 4, Week 8, Week 12 and Week 36 (end of follow-up [EOFU]).
- The time to the first Recurrence (Mycologically Proven, Presumed or Suspected) of VVC through EOFU.
- The percentage of subjects with Mycological Eradication (negative fungal culture) at Week 12, Week 24 (TOC) and Week 36 (EOFU).
- The percentage of subjects with no Mycologically Proven, Presumed or Suspected Recurrences at Week 4, Week 8, Week 12 and Week 36 (EOFU).
- The percentage of subjects with no Mycologically Proven or Presumed Recurrences at Week 4, Week 8, Week 12, TOC (Week 24) and Week 36 (EOFU).
- The proportion of subjects in three ordered categories related to the number of Recurrences (Mycologically Proven, Presumed or Suspected) of VVC from Baseline (Day 1) to TOC (Week 24) and Week 36 (EOFU). The three categories of recurrence are defined as (i) 0 to 1 episodes, (ii) 2 to 3 episodes, and (iii) ≥ 4 episodes.
- The absolute number of Mycologically Proven, Presumed or Suspected Recurrences from Baseline (Day 1) to TOC (Week 24) and Week 36 (EOFU).
- Absolute improvement in QOL outcomes at Week 12, Week 24 (TOC) and Week 36 (EOFU) as measured by EQ-5D, SF-36 and FSDS).

Safety and tolerability as measured by:

- AEs, vital signs, treatment discontinuation and safety laboratory tests at TOC (Week 24).

10.0 Study Design

10.1 Overall Description of the Study

This study is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of oral ibrexafungerp (formerly "SCY-078") compared to placebo in female subjects 12 years and older with RVVC. The primary objective of the study is

to evaluate the efficacy of oral ibrexafungerp versus placebo in preventing recurrences of VVC in subjects with RVVC based on Clinical Success.

The study will consist of a Screening visit, an Acute Phase with open-label fluconazole and a Prevention of Recurrence Phase with randomized ibrexafungerp or placebo. Screening and the beginning of the Acute Phase (Day -14) may occur on the same day. Approximately 320 subjects are planned to be enrolled into the open-label Acute Phase of the study in order to randomize approximately 240 subjects into the double-blind Prevention of Recurrence Phase, which will consist of 6 monthly, single-day treatments with randomized study drug.

A Nested Sub-Study will be made available to subjects who fail treatment with fluconazole during the Acute Phase and are not eligible for randomization into the Prevention of Recurrence Phase (see Section 21.3 [Appendix C] for Sub-Study details).

A summary of study visits is provided below. Further details of the study visits are provided in Section 10.1.1.

- **Screening (Days -16 to -14)**: To be eligible for inclusion, subjects must have a history of at least three episodes of VVC in the past 12 months (including the current episode), a total composite score ≥ 4 on the VSS Scale, a positive potassium hydroxide (KOH) test, and a normal vaginal pH (≤ 4.5). Screening and the beginning of the Acute Phase (Day -14) may occur on the same day.
- **Acute Phase (Days -14 to -1)**: Eligible subjects will receive active treatment with open-label oral fluconazole 150 mg, administered QD on Days -14, -11 and -8, for a total of 3 doses.
- **Prevention of Recurrence Phase:** The occurrence of a recurrence is the key efficacy parameter in this study. Subjects who have a culture-confirmed *Candida* spp. infection from the sample collected at Screening, achieve significant resolution of their vulvovaginal signs and symptoms (defined as a total composite score ≤ 2 on the VSS Scale) at Baseline (Day 1) and continue to meet all other eligibility criteria will be randomized into the Prevention of Recurrence Phase. Subjects who are not eligible for this study or the Nested Sub-Study will be discontinued. Subjects will be assessed for potential recurrences throughout the Study Treatment Period and the Follow-up Period.
    - **Study Treatment Period (Baseline [Day 1] through Week 24 [TOC]):** Subjects will be randomized at a 1:1 ratio to receive one of two study treatments (oral ibrexafungerp or placebo administered as a single-day treatment repeated every 4 weeks [28 days (±3)] for a total of 6 single-day treatments) in a double-blind manner. Each single-day treatment will consist of two doses of ibrexafungerp 300 mg each or placebo given 12 (±4) hours apart (total single-day ibrexafungerp dose = 600 mg). Subjects will take the study drug on Day 1 (Baseline), Week 4, Week 8, Week 12, Week 16 and Week 20, regardless of recurrence or administration of antifungal medication. Subjects will be evaluated for potential recurrence, antifungal medication use and safety throughout this period.
    - **Follow-up Period (Week 25 through Week 36 [EOFU]):** Subjects will enter the Follow-up Period regardless of recurrence or rescue antifungal medication use. Subjects will continue to be evaluated for potential recurrence, antifungal medication use and safety throughout this period.

Efficacy and Safety

Efficacy will be determined primarily by the percentage of subjects with documented Clinical Success (defined as subjects having a TOC evaluation and no Mycologically Proven, Presumed or Suspected recurrence of VVC) up to TOC (Week 24). The key secondary endpoint will be the percentage of subjects with no Mycologically Proven Recurrence (defined as an episode of VVC with a total composite score ≥ 3 on VSS Scale and a culture positive for *Candida* spp. that required antifungal treatment) at TOC (Week 24). Efficacy will also be assessed by other secondary efficacy and patient-reported outcomes (see Section 9.3).

Safety and tolerability will be evaluated throughout the study by the following parameters: AEs, treatment discontinuations, vital signs and safety laboratory tests at TOC (Week 24).

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

Study visits will consist of scheduled on-site visits, phone contacts, and lab visits (Acute Phase only), as well as unscheduled visits. Whenever possible, on-site visits and phone contacts will be scheduled to occur on the date of dosing (or as close to the date of dosing as possible) to facilitate reminding subjects to take their study doses. This is applicable for the Baseline (Day 1), Week 4, Week 8, Week 12, Week 16 (phone contact), and Week 20 (phone contact) visits.

If a subject is actively menstruating at an on-site study visit that requires a vaginal exam, the visit should be rescheduled as soon as the subject's period ends but in no case more than 7 days after the initially scheduled visit.

Phone contacts will be conducted to check for AEs, treatment compliance, potential recurrence, and concomitant medication use, including other antifungal agents. Unscheduled visits will be conducted anytime that there are symptoms indicating a potential recurrence or an AE.

Subjects will be instructed to visit the study center for a proper evaluation of any potential recurrence before initiating any VVC treatment. Subjects participating in the study will be strongly discouraged from self-administering any treatment for a potential recurrence.

An electronic dosing reminder system (e.g. text message) may be implemented for consenting subjects to facilitate study drug dosing compliance.

10.1.1.1 Screening (Days -16 to -14)

At Screening, subjects who are experiencing vulvovaginal symptoms will be evaluated by the investigator, who will obtain a vulvovaginal sample for local KOH testing and vaginal pH determination prior to initiation of open-label fluconazole treatment. The vaginal samples will also be tested for fungal culture, species identification and susceptibility testing by the central laboratory, as well as to rule out other potential pathogens. The investigators and the subjects will rate the signs and symptoms of infection, respectively, on a standardized VSS Scale. Safety

procedures, including an abbreviated physical exam, vital signs, and a urine pregnancy test will also be performed.

To be eligible for inclusion, subjects must have a history of at least three episodes of VVC in the past 12 months (including the current episode), a total composite score ≥ 4 on the VSS Scale, a positive KOH test, and a normal vaginal pH (≤ 4.5). Eligible subjects will move on to Day -14 to enter the Acute Phase of the study. The Screening and Day -14 visits may occur on the same day.

10.1.1.2 Acute Phase (Days -14 to -1)

During the Acute Phase, study visits will be scheduled on Day -14 (which may be combined with the Screening visit), Day -11 and Day -8 (phone contacts). Eligible subjects will receive active treatment with oral fluconazole 150 mg QD on Days -14, -11 and -8.

Fluconazole will be administered in an open-label fashion. Subjects will take their first dose of fluconazole at the site and self-administer the remaining doses at home. Subjects will be dispensed fluconazole supplies and subject diaries where they will rate their vulvovaginal symptoms and record dosing details, AEs and concomitant medication use.

Safety procedures (abbreviated physical exam, vital signs, AE collection) will be conducted. On Days -4 to -2 subjects will have a laboratory visit, where safety labs will be collected to be reviewed on Day 1 (Baseline) to verify eligibility, prior to randomization.

10.1.1.3 Prevention of Recurrence Phase (Day 1 [Baseline] through Week 36 [EOFU])

10.1.1.3.1 Study Treatment Period (Day 1 [Baseline] through Week 24 [TOC])

Baseline (Day 1)

On Day 1, subjects will return their open-label fluconazole supplies. Treatment compliance will be evaluated, and subject diaries will be collected and reviewed. Vulvovaginal samples will be collected for fungal culture and pH. The investigator and the subject will rate the signs and symptoms of infection, respectively, on the VSS Scale. The subject's QOL questionnaires will be administered. The results of the vaginal culture collected at Screening will be reviewed.

Subjects with a culture-confirmed *Candida* spp. infection from the sample collected at Screening who achieve a significant resolution of their vulvovaginal signs and symptoms (total composite score ≤ 2 on the VSS Scale) and continue to meet all study eligibility criteria at Baseline (Day 1) will continue to the Prevention of Recurrence Phase, where they will be randomized at a 1:1 ratio to receive one of the following two study treatments in a double-blind manner:

- Oral ibrexafungerp administered as a single-day treatment repeated every 4 weeks (28 days [±3]) for a total of 6 single-day treatments (Baseline [Day 1], Week 4, Week 8, Week 12, Week 16 and Week 20). Each single-day treatment will consist of two doses of 300 mg each given 12 (±4) hours apart (total single-day dose = 600 mg).
- Matching oral placebo administered as a single-day treatment repeated every 4 weeks (28 days [±3]) for a total of 6 single-day treatments (Baseline [Day 1], Week 4, Week 8, Week

12, Week 16 and Week 20). Each single-day treatment will consist of two doses of placebo given 12 (±4) hours apart.

Subjects will receive their first dose of study drug at the site and will be dispensed double-blind study drug and subject diaries, where they will rate their vulvovaginal symptoms on a weekly basis and at the time of each visit to the site, and will record dosing details, AEs and concomitant medication use during the study. Safety procedures (abbreviated physical exam, vital signs, AE collection and urine pregnancy test) will be conducted.

Subjects who do not have a culture-confirmed *Candida* spp. infection at Screening, do not achieve a significant resolution of their signs and symptoms at Baseline (Day 1) and/or do not continue to meet all eligibility criteria will be discontinued from the study.

A Nested Sub-Study will be made available to subjects who fail treatment with fluconazole during the Acute Phase and are not eligible for randomization into the Prevention of Recurrence Phase (see Section 21.3, Appendix C for details about the Sub-Study).

Day 2 through Week 23

On-site study visits will be scheduled at Weeks 4, 8, and 12 and phone contacts will be conducted on Weeks 16 and 20 to check for potential recurrence, treatment compliance and antifungal medication use. During this period, subjects will self-administer their double-blind study drug at home. Study drug will be taken as a single-day treatment repeated every 4 weeks (28 days [±3]) for a total of 6 single-day treatments (i.e., at Week 4, Week 8, Week 12, Week 16 and Week 20), regardless of recurrence or administration of antifungal medication, preferably with or immediately after a meal.

Subjects will be assessed for potential recurrence at all visits during the Study Treatment Period following Baseline (Day 1), including phone contacts, scheduled visits and unscheduled visits. Anytime that there is suspicion of a recurrence (Mycologically Proven, Presumed or Suspected), all procedures for the assessment of the recurrence must be completed (see Section 10.1.1.3.3 for an overview and Section 14.18 for detailed procedures). **Subjects participating in the study will be strongly discouraged from self-administering any treatment for a potential recurrence.** Subjects will be instructed to visit the study center for a proper evaluation of their recurrence before initiating any VVC treatment.

At Week 12, an abbreviated physical exam will be performed, blood samples will be drawn for safety laboratory tests and vulvovaginal samples will be collected for fungal culture and susceptibility testing by the central laboratory. The investigator and the subject will rate the signs and symptoms of infection, respectively, on the VSS Scale. Subjects will complete their QOL questionnaires. Subjects will return their empty bottles of study drug and new bottle supplies will be provided. Subject diaries will be collected, reviewed and dispensed.

Subjects will continue rating their vulvovaginal symptoms on a weekly basis and at the time of each scheduled or unscheduled visit to the site on their subject diaries and recording dosing details, AEs and concomitant medication use. AEs, concomitant medication use, treatment compliance and potential recurrence will be assessed at each study visit, including phone contacts. Subject diaries will be reviewed and vital signs will be determined at all on-site visits.

Week 24 (TOC)

At Week 24 (TOC), subjects will return any remaining medication as well as empty bottles of the study drug and treatment compliance will be evaluated. Subjects will return their diaries and diaries will be reviewed. Safety procedures (abbreviated physical exam, vital signs, AEs, and concomitant medication use) will be performed.

Vaginal samples will be obtained for fungal culture and for antifungal susceptibility testing by the central laboratory. Subjects will complete their QOL questionnaires.

The investigator and the subject will rate the signs and symptoms of infection, respectively, on the VSS Scale and potential recurrence will be assessed (see Section 10.1.1.3.3). Subjects will continue to the FU Period regardless of recurrence or antifungal medication use.

10.1.1.3.2 Follow-up Period

During the FU Period, an on-site study visit will be scheduled at Week 36 (EOFU) and phone contacts will be conducted at Weeks 28 and 32 to check for potential recurrence and antifungal medication use. Subjects will continue to rate their vulvovaginal symptoms on a weekly basis and at the time of each scheduled or unscheduled visit to the site and will continue to record use of any antifungal medication on their subject diaries.

Subjects will be assessed for potential recurrence at all visits during the Follow-up Period, including phone contacts, scheduled visits and unscheduled visits. Anytime that there is suspicion of a recurrence, all procedures for the assessment of the recurrence must be completed (see Section 10.1.1.3.3 for an overview and Section 14.18 for detailed procedures). **Subjects participating in the study will be strongly discouraged from self-administering any treatment for a potential recurrence.** Subjects will be instructed to visit the study center for a proper evaluation of their recurrence before initiating any VVC treatment.

At the EOFU (Week 36) visit, vaginal samples will be obtained for fungal culture and for antifungal susceptibility testing by the central laboratory. Subjects will complete their QOL questionnaires and subject diaries will be reviewed and collected. Safety procedures (vital signs, AEs, and concomitant medication use) will be performed. Blood samples will be drawn if needed to follow up on a laboratory abnormality.

Subjects will continue to complete all FU visits regardless of recurrence or antifungal medication use.

10.1.1.3.3 Recurrence During the Prevention of Recurrence Phase

The occurrence of a recurrence is the key efficacy parameter in this study. Randomized subjects will be assessed for potential recurrence at all visits during the Prevention of Recurrence Phase following Day 1 (Baseline) (i.e., from Day 2 through Week 36 [EOFU]), including phone contacts, scheduled visits and unscheduled visits, as well as in between visits. If during a phone contact or at any other time there is suspicion of a potential recurrence (any kind of recurrence, i.e., Mycologically Proven, Presumed or Suspected), subjects will be instructed to visit the study center for a proper evaluation of their recurrence before initiating any VVC treatment**.**

Potential recurrences will be assessed based on clinical and mycological outcomes and need for other antifungal treatment. If a subject has symptoms suggestive of *Candida* infection (itching, burning, irritation) that in the opinion of the investigator may require antifungal therapy, the following procedures must be completed:

- Rate and document symptoms in the electronic case report form (eCRF),
- Perform vaginal examination to rate signs and document in the eCRF,
- Measure vaginal pH at the site and document results in the eCRF,
- Collect vaginal sample for KOH testing and investigation of potential bacterial vaginosis and *Trichomonas vaginalis* infection at the site or by the local laboratory, and
- Collect vaginal samples for fungal culture by the central laboratory.

All of the procedures above should be completed prior to administration of rescue antifungal medication. Subjects participating in the study should be strongly discouraged from self-administering any treatment for a potential recurrence. Ideally, if the severity of the symptoms allows based on the investigator's judgment, the initiation of antifungal therapy should be delayed until results from the vaginal culture are available to confirm that the episode is due to *Candida* spp. and not to other cause of vaginitis.

See Section 14.18 for a detailed description of procedures to be completed for potential recurrences.

In this study, Recurrences of VVC will be broken into three categories:

- **Mycologically Proven Recurrence:** An episode of VVC with a total composite score ≥ 3 on the VSS Scale and a culture positive for *Candida* spp. that required antifungal treatment.
- **Presumed Recurrence:** An episode of VVC with a total composite score ≥ 3 on the VSS Scale that required antifungal treatment and for which there is a positive KOH microscopy but no positive fungal culture.
- **Suspected Recurrence**: An episode of VVC that required treatment with an antifungal agent (including self-administration with over-the-counter antifungals) regardless of VSS composite score but for which there is no mycological evidence of disease, such as a positive KOH microscopy or fungal culture.

Subjects with a **Mycologically Proven Recurrence** should receive antifungal therapy.

If a subject experiences one or more recurrences during the Study Treatment Period Phase (i.e., either a Mycologically Proven Recurrence, a Presumed Recurrence or a Suspected Recurrence), she will continue her scheduled study drug administration and will complete all scheduled visits until reaching EOFU.

All antifungal therapy administered during the study should be documented in the electronic data capture (EDC) system, with the reason for use clearly indicated (i.e., Mycologically Proven Recurrence, Presumed Recurrence, Suspected Recurrence).

10.1.2 Study Assessments

The study will include efficacy, safety and tolerability assessments.

Efficacy Assessments

Efficacy assessments will be based on clinical evaluations, mycological testing and QOL. The primary efficacy endpoint of the study is the percentage of subjects with documented Clinical Success (defined as subjects having a TOC evaluation and no Mycologically Proven, Presumed

or Suspected Recurrence of VVC) up to TOC (Week 24). The key secondary efficacy endpoint is the percentage of subjects with no Mycologically Proven Recurrence (defined as an episode of VVC with a total composite score ≥ 3 on the VSS Scale and a culture positive for *Candida* spp. that required antifungal treatment) at TOC (Week 24). Efficacy will also be assessed by other secondary efficacy and patient-reported outcomes (see Section 9.3).

Clinical Evaluations

The signs (edema, erythema and excoriation or fissures) and symptoms (itching, burning and irritation) of infection will be assessed by the investigator and the subject, respectively, on the VSS Scale (provided in Appendix B). The VSS Scale is a standardized, predefined scale where each sign and symptom will be given a numerical rating based on severity (absent = 0; mild = 1; moderate = 2; severe = 3) to calculate a total composite VSS score. The symptoms of infection will be rated by the subject on a weekly basis and at the time of each scheduled or unscheduled visit to the site throughout the Prevention of Recurrence Phase. Vaginal examinations will be conducted by the investigator to rate the subject's signs of infection at protocol-specified visits and anytime that there is suspicion of a potential recurrence.

Mycological Testing

Mycological tests will include direct wet mount microscopic examination to visualize clue cells indicative of bacterial vaginosis or trichomonas, direct microscopic examination with 10% KOH to identify yeast, and fungal cultures. The direct wet mount and KOH examination will be performed locally at Screening for the determination of subject eligibility and then anytime that a recurrence is suspected. 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. Fungal cultures will be performed centrally at Screening and at protocol-specified time points for species identification and susceptibility testing. Fungal cultures will also be done anytime that a recurrence is suspected during the Prevention of Recurrence Phase and for antifungal susceptibility testing for subjects with positive cultures.

Quality of Life

QOL will be assessed by EQ-5D, SF-36 and FSDS at protocol-specified time points to assess improvement in QOL outcomes.

Safety Assessments

Safety procedures will include collection of AEs, treatment discontinuations, abbreviated 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 320 subjects are planned to be enrolled into the open-label Acute Phase of the study in order to randomize approximately 240 subjects at a 1:1 ratio to one of the two study treatment groups. All randomization of subjects will be managed electronically through an interactive voice response system (IWRS).

Subjects will be stratified at randomization based on the presence or absence of uncontrolled diabetes mellitus, defined as A1C levels ≥ 8.00% at Baseline (Uncontrolled diabetes mellitus: YES or NO), and by geographical region (USA or Ex-USA).

10.3 Study Duration

Each subject is expected to complete the study within approximately 38 weeks.

10.4 Number of Centers

Approximately 50 study centers are expected to participate in the study.

11.0 Study Population

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

11.1 Inclusion Criteria

Subjects must fulfill all the following criteria at Screening and/or Baseline to be eligible for study admission:

1. Subject is a postmenarchal female subject 12 years and older at Screening 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 prior to administration of the initial dose of study drug.
2. Subject has a diagnosis of symptomatic VVC that meets the following criteria at Screening:
   a. A total composite score of ≥ 4 on the VSS Scale
   b. Positive microscopic examination with 10% KOH in a vaginal sample collected at Screening revealing yeast forms (hyphae/pseudohyphae) or budding yeasts
   c. Normal vaginal pH (≤ 4.5)
   d. A minimum of three episodes of VVC in the past 12 months, including the current episode, that required administration of antifungal medication. Besides the current episode, at least one of the previous episodes in the past 12 months is required to have been a physician-diagnosed episode of VVC, with at least one positive test confirming vaginal yeast infection (e.g., KOH, culture or fungal polymerase chain reaction)
3. Subject meets the following criteria at Baseline (Day 1):
   a. Significant resolution of signs and symptoms of *Candida* infection (total composite score ≤ 2 on the VSS Scale)
   b. Culture positive for *Candida* spp. in a vaginal sample collected at Screening
   c. Normal vaginal pH (≤ 4.5)
4. Subject is able to take oral tablets and capsules.

5. 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, systemic hormonal contraceptives (i.e., 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. Subjects who are taking hormonal contraceptives must use a non-hormonal barrier method of contraception until 10 days after the last dose of study drug. 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 method 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.

      Note: Subjects must refrain from using any topical vaginal contraceptives such as spermicides or intra-vaginal hormonal contraceptive devices such as vaginal rings as these may interfere with the efficacy evaluations.

      Note: Women of childbearing potential must have a negative urine pregnancy test (sensitivity ≥25 mIU/human chorionic gonadotropin [hCG]) prior to enrollment at Screening and at Baseline (performed by the site's local laboratory).

6. Subject and/or parent/legal representative 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 and able to sign the subject's ICF.
7. 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 United States Health Information Portability and Accountability Act Authorization form).
8. 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 any of the following exclusion criteria:

1. Subject has any vaginal condition other than RVVC 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, Herpes* virus, *Neisseria gonorrhoeae, Chlamydia*, symptomatic human papillomavirus infection or other mixed infections.
2. Subject received systemic and/or topical vaginal antifungal treatment, including prescription or over-the-counter products, within 28 days prior to the Day -14 visit.
3. Subject is receiving or anticipates to require 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 topical vaginal antifungal treatment other than study drug and rescue medication (if needed), as specified in the protocol, anytime during the study.
    b. Select CYP3A4/5 inducers during the 14 days prior to enrollment and during study treatment.
    c. Select strong CYP3A4/5 inhibitors during 48 hours prior to enrollment and during study treatment.
    d. Select P-gp substrates during the 48 hours prior to enrollment or during study treatment with ibrexafungerp.
    e. Topical vaginal corticosteroids from 7 days prior to the Screening visit to the Week 24 (TOC) visit.
4. Subject has active menstruation at the Screening visit. **Note:** The Screening visit may be rescheduled if required.
5. Subject has a history of or an active cervical/vaginal cancer.
6. Subject has a known hypersensitivity to fluconazole or any of the components of the fluconazole or ibrexafungerp formulations.
7. Subject has a known human immunodeficiency virus infection and/or is receiving chemotherapy, has recently received immunosuppressive or systemic corticosteroid therapies, or has an illness that, in the judgment of the investigator, is serious enough to induce an immune deficiency.
8. Subject has had any major illness within 30 days before Screening.
9. Subject has participated in any other investigational study within at least 30 days (or 5.5 half-lives of the investigational product, whichever is longer) before signing the ICF.
10. Subject has received prior treatment with the study drug in a previous trial.
11. Subject has any other condition or laboratory abnormality evidencing a major organ system disease that, in the judgment of the investigator, would put the subject at unacceptable risk for participation in the study or may interfere with the assessments included in the study.

12. Subject 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.
13. 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 subject's legal guardian;
- 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).

A subject will be discontinued from the study for any of the following reasons:

- Absence of culture-confirmed *Candida* spp. infection from the sample collected at Screening as reviewed at Baseline (Day 1)
- Failure to continue to meet all eligibility criteria at Baseline (Day 1)
- Occurrence of pregnancy

A subject will be discontinued from the study and will enter the Nested Sub-Study (see Section 21.3 [Appendix C]) for the following reason:

- Positive fungal cultures at Screening with persistence of signs and symptoms of infection (total composite score ≥ 3 on the VSS Scale) at Baseline (Day 1), following treatment with open-label fluconazole

Subjects with Recurrences (Mycologically Proven, Presumed or Suspected) of VVC will not be discontinued from the study but will receive rescue antifungal medication, continue their study drug administration (if during the Study Treatment Phase) and complete all their scheduled visits until reaching EOFU.

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). At the time of discontinuation, all Week 24 (TOC) procedures should be performed for subjects who discontinue from the study on or before the Week 24 (TOC) visit and all Week 36 (EOFU) procedures should be performed for subjects who discontinue from the study after the TOC visit but on or before the EOFU visit.

11.4 Replacement of Discontinued Subjects

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

12.0 Study Treatments

12.1 Study Treatment Groups

12.1.1 Acute Phase

Subjects who meet all study eligibility criteria at Screening will enter the Acute Phase of the study and will receive oral fluconazole, as follows:

- Oral fluconazole 150 mg QD on Days -14, -11 and -8

The first dose of fluconazole will be administered on Day -14 at the study site, after all other visit procedures have been done. Subjects will self-administer the remaining doses at home.

12.1.2 Prevention of Recurrence Phase

Subjects who have a culture-confirmed VVC from the sample collected at Screening, achieve a significant resolution of the signs and symptoms of infection (total composite score ≤ 2 on the VSS Scale) at Baseline (Day 1) and continue to meet all study eligibility criteria will be randomized at a 1:1 ratio to one of the following two treatment groups:

- Oral ibrexafungerp administered as a single-day treatment repeated every 4 weeks (28 days [±3]) for a total of 6 single-day treatments (Baseline [Day 1], Week 4, Week 8, Week 12, Week 16 and Week 20). Each single-day treatment will consist of two doses of 300 mg each given 12 (±4) hours apart (total single-day dose = 600 mg) (see Table 1).
- Matching oral placebo administered as a single-day treatment repeated every 4 weeks (28 days [±3]) for a total of 6 single-day treatments (Baseline [Day 1], Week 4, Week 8, Week 12, Week 16 and Week 20). Each single-day treatment will consist of two doses of placebo given 12 (±4) hours apart.

Table 1: Double-Blind Oral Ibrexafungerp Dosing Regimen

Dosing Day	Study Visit/Study Day	Single-Day Doses	Oral Tablets	Total Daily Dose
Dosing Day 1	Week 1/ Study Day 1 (Baseline)	300 mg AM 300 mg PM	2 x 150 mg 2 x 150 mg	600 mg
Dosing Day 2	Week 4/ Study Day 28 (±3)	300 mg AM 300 mg PM	2 x 150 mg 2 x 150 mg	600 mg
Dosing Day 3	Week 8/ Study Day 56 (±3)	300 mg AM 300 mg PM	2 x 150 mg 2 x 150 mg	600 mg
Dosing Day 4	Week 12/ Study Day 84 (±3)	300 mg AM 300 mg PM	2 x 150 mg 2 x 150 mg	600 mg
Dosing Day 5	Week 16/ Study Day 112 (±3)	300 mg AM 300 mg PM	2 x 150 mg 2 x 150 mg	600 mg
Dosing Day 6	Week 20/ Study Day 140 (±3)	300 mg AM 300 mg PM	2 x 150 mg 2 x 150 mg	600 mg

Subjects will receive their first dose of double-blind study drug at the site and will self-administer the remaining doses at home. Subjects must take the two doses of study drug 12 hours apart (±4 hours), preferably with or immediately after a meal. An electronic dosing reminder system (e.g. text message) may be implemented for consenting subjects to facilitate study drug dosing compliance.

12.2 Dietary Requirements

Double-blind study drug should be administered preferably with or immediately after a meal. In addition, it is recommended that each subject identifies and keeps their optimal routine to facilitate compliance (for example, administering the study drug at breakfast and at dinner on treatment days).

12.3 Study Drugs

Study drug will consist of oral ibrexafungerp (150-mg tablets) and ibrexafungerp matching oral placebo tablets for the double-blind Prevention of Recurrence Phase, and oral fluconazole (150-mg tablets or capsules) for the open-label Acute Phase. Study drug will be provided by the Sponsor.

12.3.1 Ibrexafungerp (SCY-078) Description

Study Drug Identifier: Ibrexafungerp (SCY-078)

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

Molecular Weight: 922.18 (citrate salt)

Physical Description: White to off-white solid

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

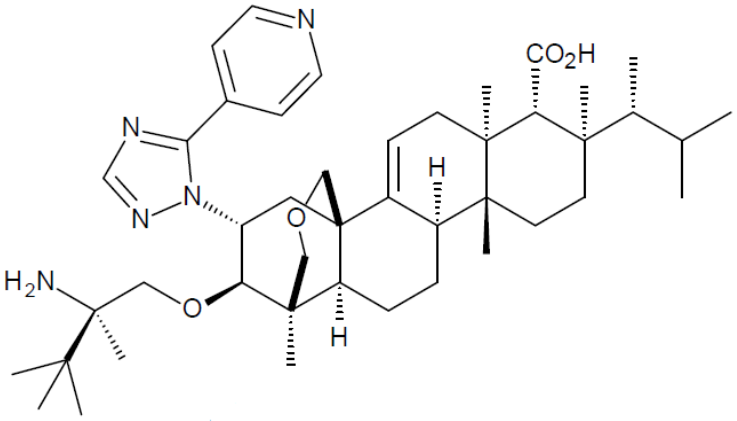


Figure 2 Chemical Structure of Ibrexafungerp (SCY-078) Citrate

12.3.2 Formulation, Packaging and Labelling

Study drug will consist of fluconazole, ibrexafungerp (SCY-078) and ibrexafungerp-matching placebo.

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.

Fluconazole drug product will be sourced commercially and will be provided as a tablet or capsule containing 150 mg of active ingredient.

The placebo product matching ibrexafungerp will be supplied as an oral 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.

Ibrexafungerp and matching placebo drug supplies will be packaged in bottles. Bottles will contain 12 oral tablets of either ibrexafungerp or matching placebo. Bottles will be supplied at Baseline (Day 1) and Week 12. 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 will include the following information and any other information required by applicable regulations:

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

12.3.3 Storage and Stability

The pharmacist or appropriate designee at each clinical research site will be responsible for the study drug. For long-term storage at the site, ibrexafungerp and matching placebo supplies (provided in bottles) and fluconazole supplies (provided in their original commercial packaging for each region [e.g., blister pack or bottle]) must be kept in a secure area (e.g., locked cabinet) and stored at room temperature.

12.4 Drug Accountability

The investigator or designee will inventory and acknowledge receipt of all shipments of the study drug. An IWRS will be used to dispense study drugs to individual subjects during the Prevention of Recurrence Phase. 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. After 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 during the double-blind phase of the study. 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 or capsules
    - All product quality complaints should be reported to the Sponsor
- Collect and count the number of fluconazole tablets/capsules remaining at the Baseline (Day 1) visit

- Collect and count the number of double-blind tablets remaining at the Week 12 and Week 24 (TOC) visits
- Review subject diary and tablet/capsule count, 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

Compliance for open-label fluconazole treatment during the Acute Phase of the study will be reviewed at Baseline (Day 1). Treatment compliance with double-blind study drug will be reviewed at all study visits during the Study Treatment Period, including on-site visits and phone contacts.

Subjects (or subject's parent/legal representative, if applicable) will be instructed to have the assigned bottles or other containers of study medication (including empty bottles/containers) with them at these visits. Compliance will be assessed based on remaining tablets/capsules 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. 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 AEs related with tolerability.

13.0 Non-Study Treatments

13.1 Prior and Concomitant Medications

All medications (including prescription and over-the-counter medications, supplements, and herbal products) taken from 28 days before Screening through the Week 24 (TOC) visit will be recorded on the eCRF. Only the use of other antifungal medications, medications used to treat vaginal bacterial or parasitic infections, topical vaginal medications or medications to treat a study-drug related AE will be recorded after the TOC visit through the last study visit (Week 36 [EOFU]). Start and stop dates of concomitant medications will be recorded on the eCRF. Prior and concomitant medications will be reviewed and recorded at all scheduled and unscheduled study visits.

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

13.2 Prohibited Medications

Medications specifically not permitted in the inclusion and/or exclusion criteria (Section 11.1 and Section 11.2, respectively) include the following:

- Non-study systemic or topical vaginal antifungal therapy
- Topical vaginal corticosteroids and topical vaginal contraceptives or intra-vaginal hormonal contraceptive devices

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

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 with a narrow therapeutic window, including but not limited to sirolimus, cyclosporine, tacrolimus and warfarin
- Organic anion-transporting polypeptide 1B3 (OATP1B3) substrates

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

13.4 Study Restrictions

There are no 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 Section 15.0. Study days and weeks are counted relative to the first dose of double-blind study drug (Baseline [Day 1]).

Study visits will consist of scheduled on-site visits, phone contacts, and lab visits (Acute Phase only) and unscheduled visits. Screening will occur on Days -16 to -14. The Acute Phase will comprise Day -14 to Day -1 (+3). The Screening and Day -14 visits may occur on the same day. On-site study visits during the Prevention of Recurrence Phase (i.e., Baseline [Day 1], Week 4, Week 8, Week 12, Week 24 and Week 36) will have a window of ±3 days.

Whenever possible, on-site visits and phone contacts will be scheduled to occur on the date of dosing (or as close to the date of dosing as possible) to facilitate reminding subjects to take their study doses. This is applicable for the Baseline (Day 1), Week 4, Week 8, Week 12, Week 16 (phone contact), and Week 20 (phone contact) visits. An electronic dosing reminder system (e.g. text message) may be implemented for consenting subjects to facilitate study drug dosing compliance.

If a subject is actively menstruating at an on-site study visit that requires a vaginal exam, the visit should be rescheduled as soon as the subject's period ends but in no case more than 7 days after the initially scheduled visit.

Phone contacts will be conducted to check for AEs, treatment compliance, potential recurrence, and concomitant medication use, including other antifungal agents. Unscheduled visits will be

conducted anytime that there are symptoms indicating a potential recurrence or an AE. If during a phone contact or at any other time there is suspicion of a potential recurrence (any kind of recurrence, i.e., Mycologically Proven, Presumed or Suspected), subjects will be strongly discouraged from self-administering any treatment and will be instructed to visit the study center for a proper evaluation of their recurrence before initiating any VVC treatment.

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. Additional local regulatory requirements may be applicable for participation of subjects under the age of consent. At Screening, subjects will provide consent for participation in both this study and the Nested Sub-Study, and will enter either study based on the criteria met at Baseline.

14.2 Assignment of Subject Number

At Screening, all subjects who have signed an ICF will receive a unique subject identification (ID) number. The subject numbers assigned to eligible subjects will be recorded in the eCRF. This number will be unique to each subject and will be used to identify the subject throughout the study. This number is different from the treatment bottle number.

Subjects who are screen failures or who are not eligible for randomization into the Prevention of Recurrence Phase 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 study eligibility 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 for the study 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, Baseline (Day 1), Week 12 and Week 24 (TOC). Abbreviated physical exams may also be conducted at unscheduled visits, if needed.

14.6 Urine Pregnancy Test

A urine pregnancy test will be performed at Screening, Baseline (Day 1) and unscheduled visits (if needed) by the local laboratory for all subjects of childbearing potential. The urine test will have a sensitivity to detect hCG levels of at least the 25 mIU/hCG threshold. Subjects must have a negative pregnancy test at Screening and Baseline (Day 1) before starting the study drug.

14.7 Vulvovaginal Samples

The following vulvovaginal samples will be collected during the study:

- **Sample for direct microscopic examination with 10% KOH:** to be collected at the Screening visit and any time that a subject experiences a potential recurrence (including both scheduled and unscheduled visits). The sample will be assessed by a local laboratory or at the site by the investigator or a qualified designee. The direct microscopic examination with KOH is intended for the visualization of yeasts.
- **Sample for fungal culture**: to be collected at Screening, Baseline (Day 1), Week 12, Week 24 (TOC), Week 36 (EOFU) and any time that a subject experiences a potential recurrence (including both scheduled and unscheduled visits). The sample will be processed by a central laboratory for species identification. Positive cultures will also be tested for susceptibility against ibrexafungerp, fluconazole and additional antifungal agents, as deemed appropriate based on validated methods.
- **Sample for vaginal pH:** to be collected at Screening, Baseline (Day 1) and any time that a subject experiences a potential recurrence. The sample will be assessed at the site by the investigator or a qualified designee.
- Sample for identification of other pathogens:
    - Samples (e.g. wet mount) to rule out bacterial vaginosis and *Trichomonas vaginalis* will be collected at the Screening visit and any time that a subject experiences a potential recurrence (including both scheduled and unscheduled visits). Samples will be assessed by a local laboratory or at the site by the investigator or a qualified designee.
    - Samples to rule out *Neisseria Gonorrhoeae, Chlamydia trachomatis* or *Herpes* virus to be collected at the Screening visit and any time that a subject experiences a potential recurrence (including both scheduled and unscheduled visits) if any of these pathogens is suspected. Samples will be processed by a central laboratory.

If during a phone contact or at any other time there is suspicion of a potential recurrence (any kind of recurrence, i.e., Mycologically Proven, Presumed or Suspected), subjects will be strongly discouraged from self-administering any treatment and will be instructed to visit the study center immediately for collection of vulvovaginal samples before initiating any VVC treatment. Procedures for collecting and processing local samples, as well as for shipping central laboratory vulvovaginal samples, will be described in the laboratory manual.

14.8 Vulvovaginal Examination and Rating of 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 Screening, Baseline (Day 1), Week 12 and Week 24 (TOC). The signs of infection will also be rated at Week 4, Week 8 and Week 36 (EOFU) if symptoms are present and any time there is suspicion of a potential recurrence. A vulvovaginal examination should be scheduled immediately if there is suspicion of a potential recurrence based on a phone contact discussion or at any other time (see Section 14.18). The investigator should ensure that subjects rate their symptoms of infection at the site every time that the investigator performs a vulvovaginal examination for the rating of signs.

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.

If a subject is actively menstruating at the time of an on-site study visit that requires a vulvovaginal exam, the visit should be rescheduled as soon as the subject's period ends but in no case more than 7 days after the initially scheduled visit.

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

Subjects will be asked to rate their vulvovaginal symptoms at Screening, from Day -14 through Day -1 of the Acute Phase, and then from Day 1 (Baseline) through Week 36 (EOFU) of the Prevention of Recurrence Phase. Subjects will also assess their symptoms at unscheduled visits, if applicable.

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

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

From Baseline (Day 1) through the Week 36 (EOFU) visit, subjects will rate their symptoms and record their scores on the VSS Scale included in their subject diaries. Symptoms of infection will be rated on a weekly basis and at the time of each scheduled or unscheduled visit to the site.

14.10 Dispensing and Dosing of Open-Label Fluconazole

On Day -14, eligible subjects (or subjects' legal representatives, if applicable) will be dispensed commercially sourced open-label fluconazole (see Section 12.3.2). All eligible subjects who

enter the Acute Phase of the study will receive oral fluconazole 150 mg QD on Days -14, -11 and -8 (Section 12.1.1). The first dose of fluconazole will be administered at the site on Day -14, after all other visit procedures have been done. The remaining doses will be self-administered by the subjects at home. An electronic dosing reminder system (e.g. text message) may be implemented for consenting subjects to facilitate study drug dosing compliance.

14.11 Dispensing, Completion, Review and Collection of Subject Diaries

All subjects will receive subject diaries that they will complete once a week from Day -14 to Day -1 of the Acute Phase and from Day 1 (Baseline) through Week 36 (EOFU) of the Prevention of Recurrence Phase of the study.

Diaries will be dispensed to all subjects on Day -14. At the Baseline (Day 1) visit of the study:

- Subjects who do not meet criteria to enter the Prevention of Recurrence phase of the study or to enter the Nested Sub-Study will be discontinued from the study and will have their diaries collected at that visit.
- Subjects who do not meet all criteria to enter the Prevention of Recurrence phase of the study but meet eligibility for the Nested Sub-Study will have their diaries e collected for review and redispensed at the Sub-Study Baseline visit (see Sub-Study details in Section 21.3 [Appendix C]).
- Subjects who are eligible to enter the Prevention of Recurrence Phase of the study will have their diaries collected and dispensed every three 4-week period, i.e., at Baseline (Day 1), Week 12, Week 24 (TOC), Week 36 (EOFU, diary collection only).

Subject diaries will be reviewed at all on-site visits (Baseline [Day 1], Week 4, Week 8, Week 12, Week 24 [TOC], Week 36 [EOFU]) and unscheduled visits.

The subject diaries will include the Vulvovaginal Signs and Symptoms (VSS) Scale so that subjects can rate their vulvovaginal symptoms (see Section 14.9 for symptom rating procedures and Section 21.2 [Appendix B] for the full VSS Scale). Subjects will record the date of study medication dosing, vulvovaginal symptoms rated on a weekly basis and at the time of each scheduled or unscheduled visit to the site, other medical concerns or complaints and concomitant medications used.

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 reviewed by the site and relevant findings will be included in the corresponding eCRFs modules (e.g. concomitant medications, AEs, etc.).

14.12 Sample Collection for Safety Laboratory Tests

Safety laboratory tests will be performed by a qualified central laboratory. Blood samples for safety laboratory tests will be collected at the Days -4 to -2 visit (Acute Phase, lab visit only) to determine subject eligibility. Lab results will be reviewed at Baseline (Day 1). Additional samples will be collected at Week 12 and at unscheduled visits, if needed. If indicated, these may be done at Week 36 to follow up on 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
- Hemoglobin A1C (glycosylated hemoglobin)
- Albumin
- Sodium
- Potassium
- Alkaline Phosphatase
- Creatinine
- Blood Urea Nitrogen (BUN)
- Total creatine phosphokinase (CPK)
- Aspartate aminotransferase (AST/SGOT)
- Alanine aminotransferase (ALT/SGPT)
- Gamma glutamyl transferase (GGT)
- Bilirubin (total, direct and indirect)
- Total protein

14.13 Collection of Open-Label Fluconazole Supplies and Evaluation of Treatment Compliance

Treatment compliance with open-label fluconazole dosing during the Acute Phase will be reviewed by the investigator or designee at Baseline (Day 1). Subjects will be instructed to bring all fluconazole supplies (including empty bottles/containers) with them to assess medication compliance. Further details are available in Section 12.5.

14.14 Assessment of Clinical Outcome following Fluconazole Treatment

At the Baseline (Day 1) visit of the study, the investigator will assess the subject's signs and symptoms of infection based on the VSS Scale ratings to determine if the subject achieved a significant resolution of all signs and symptoms of infection (total composite score ≤ 2 on the VSS Scale) and may enter the Prevention of Recurrence Phase or if the subject did not achieve a significant resolution of her signs and symptoms of infection but meets other criteria to enter the open-label, ibrexafungerp, Nested Sub-Study (see Section 21.3 [Appendix C] for details regarding the Sub-Study). Subjects who do not meet criteria for this study or the Sub-Study will be discontinued.

14.15 Randomization

At Baseline (Day 1), subjects with a culture-confirmed *Candida* spp. infection from a sample collected at Screening who achieve a significant resolution of their signs and symptoms and continue to meet all study eligibility criteria will continue to the Prevention of Recurrence Phase, where they will be randomized at a 1:1 ratio to one of the two study treatment groups. Subjects will be stratified at randomization based on the presence or absence of uncontrolled diabetes mellitus, defined as A1C levels ≥ 8.00% at Baseline (Uncontrolled diabetes mellitus: YES or NO), and by geographical region (USA or Ex-USA).

Subject randomization will be performed using an IWRS, which will assign a unique randomization number for each randomized subject corresponding to a study treatment. Only one randomization number and study drug treatment will be assigned to each eligible subject.

14.16 Dispensing and Dosing of Blinded Study Drug

At Baseline (Day 1), eligible subjects will be dispensed bottles containing double-blind study medication supplies for 12 weeks (see Section 12.3.2). At Week 12, subjects will return all their bottles of study drug (see Section 14.19) and will be dispensed new supplies for an additional 12-week period.

Study drug will be taken as a single-day treatment repeated every 4 weeks (28 days [±3]) for a total of 6 single-day treatments (Baseline [Day 1], Week 4, Week 8, Week 12, Week 16 and Week 20). The first dose of double-blind study drug will be administered at the study site (Baseline [Day 1]) and the remaining doses will be self-administered by the subjects at home, preferably with or immediately after a meal.

Whenever possible, on-site visits and phone contacts will be scheduled to occur on the date of dosing to facilitate reminding subjects to take their study drug dose. It is recommended that each subject identifies and keeps their optimal routine to facilitate compliance (for example, administering the study drug after breakfast and after dinner on dosing days). An electronic dosing reminder system (e.g. text message) may be implemented for consenting subjects to facilitate study drug dosing compliance. Details of study treatment groups and dietary requirements for treatment administration are provided in Section 12.1.2 and Section 12.2, respectively.

14.17 Assessment of Quality of Life

QOL will be assessed at Day -14, Baseline (Day 1), Week 12, Week 24 (TOC) and Week 36 (EOFU). Quality-of-life tools will include the Euro Quol 5 Dimensions (EQ-5D), Short Form Health Survey (SF-36) and Female Sexual Distress-Revised Scale (FSDS).

14.18 Assessment of Potential Recurrence and Use of Rescue Antifungal Medication

The occurrence of a recurrence is the key efficacy parameter in this study. Randomized subjects will be assessed for potential recurrence at all visits during the Prevention of Recurrence Phase following Day 1 (Baseline) (i.e., from Day 2 through Week 36 [EOFU]), including phone

contacts, scheduled visits and unscheduled visits, as well as in between visits. If during a phone contact or at any other time there is suspicion of a potential recurrence (any kind of recurrence, i.e., Mycologically Proven, Presumed or Suspected), subjects will be instructed to visit the study center for a proper evaluation of their recurrence before initiating any VVC treatment.

14.18.1 Categories of Recurrences

In this study, Recurrences of VVC will be broken into three categories:

- **Mycologically Proven Recurrence:** An episode of VVC with a total composite score ≥ 3 on the VSS Scale and a culture positive for *Candida* spp. that required antifungal treatment.
- **Presumed Recurrence:** An episode of VVC with a total composite score ≥ 3 on the VSS Scale that required antifungal treatment and for which there is a positive KOH microscopy but no positive fungal culture.
- **Suspected Recurrence**: An episode of VVC that required treatment with an antifungal agent (including self-administration with over-the-counter antifungals) regardless of VSS composite score but for which there is no mycological evidence of disease, such as a positive KOH microscopy or fungal culture.

14.18.2 Procedures for Potential Recurrences

Potential recurrences will be assessed based on clinical and mycological outcomes and need for other antifungal treatment. If a subject has symptoms suggestive of *Candida* infection (itching, burning, irritation) that in the opinion of the investigator may require antifungal therapy, the following procedures must be completed:

- Rate and document symptoms in the eCRF (Section 14.9),
- Perform vaginal examination to rate signs and document in the eCRF (Section 14.8),
- Measure vaginal pH at the site and document results in the eCRF (Section 14.7),
- Collect vaginal sample for KOH testing and investigation of potential bacterial vaginosis and *Trichomonas vaginal* infection at the site or by the local laboratory (Section 14.7),
- Collect vaginal samples for fungal culture by the central laboratory (Section 14.7), and
- Document any additional antifungal treatment used by the subjects (Section 14.21).

All of the procedures above should be completed prior to administration of rescue antifungal medication. **Subjects participating in the study should be strongly discouraged from self-administering any treatment for a potential recurrence.** Ideally, if the severity of the symptoms allows based on the investigator's judgment, the initiation of antifungal therapy should be delayed until results from the vaginal culture are available to confirm that the episode is due to *Candida* spp. and not to other cause of vaginitis.

The following steps should be followed for potential recurrences:

- If the vaginal culture results are positive for yeast and the subject remains symptomatic (VSS score ≥3), rescue antifungal therapy should be offered and the episode should be listed as a Mycologically Proven Recurrence. Rescue antifungal therapy should be documented in the eCRF.
- If the vaginal culture results are negative for yeast, other causes of vaginitis (e.g. bacterial vaginitis or trichomoniasis) should be further investigated and rescue antifungal therapy may not be indicated. Subjects with a diagnosis of vaginitis caused by pathogens other than yeast (e.g. bacterial vaginitis or trichomoniasis) may receive treatment for these conditions as indicated and the vaginitis episode should be listed as AE.
- If the vaginal culture results are negative for yeast but the patient was given rescue antifungal therapy based on KOH results and symptoms (VSS score ≥3), the episode should be listed as a Presumed Recurrence. The rescue antifungal therapy administered should be documented in the eCRF.
- Empiric administration of rescue antifungal therapy prior to collecting and documenting evidence that the vaginal symptoms are caused by *Candida* spp. infection is strongly discouraged. Subjects who receive empiric rescue antifungal therapy for a potential recurrence of VVC prior to documenting the *Candida* spp. infection should still have their vaginal evaluation including KOH and culture collected as soon as possible. These episodes should be listed as Suspected Recurrences.
- If subjects experience a relapse of the VVC symptoms, they should be strongly discouraged from self-administering any treatment for VVC and instructed to visit the study site for evaluation of the episode and prescription of rescue therapy, if needed.
- In the event that the subject self-administers, or another physician prescribes therapy for a recurrent episode of VVC, the subject should still be seen at the study site as soon as possible for an unscheduled visit, which should include collection of a vaginal swab for culture.

14.18.3 Rescue Antifungal Therapy

Subjects will be offered one dose of fluconazole 150 mg as rescue therapy. Other antifungal rescue therapy may be administered, per investigator's discretion, based on the *Candida* species reported from the culture results. All antifungal therapy administered during the study should be documented in the EDC, with the reason for use clearly indicated (i.e., Mycologically Proven Recurrence, Presumed Recurrence or Suspected Recurrence).

If a subject experiences one or more recurrences during the Study Treatment Period (i.e., a Mycologically Proven Recurrence, a Presumed Recurrence or a Suspected Recurrence), she will continue her scheduled study drug administration and will complete all scheduled visits until reaching EOFU.

14.19 Collection of Blinded Study Drug Supplies and Evaluation of Treatment Compliance

Treatment compliance with double-blind study drug will be reviewed by the investigator or designee at all study visits during the Study Treatment Period, including both on-site visits and phone contacts. Subjects (or subjects' legal representatives, if applicable) will be instructed to bring all bottles (including empty bottles) of study medication with them at all visits to assess medication compliance. Empty bottles will be collected at Week 12 and Week 24 (TOC). Further details are available in Section 12.5.

14.20 Vital Signs

Vital signs, including blood pressure (systolic and diastolic), heart rate, respiratory rate and body temperature will be measured at all on-site scheduled and unscheduled visits.

14.21 Prior and Concomitant Medication Review

All medications (including prescription and over-the-counter medications, supplements, and herbal products) taken from 28 days before Screening through the Week 24 (TOC) visit will be recorded on the eCRF. Only the use of other antifungal medications, medications used to treat vaginal bacterial or parasitic infections, topical vaginal medications or medications to treat a study-drug related AE will be recorded after the TOC visit through the last study visit (Week 36 [EOFU]). Start and stop dates of concomitant medications will be recorded on 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.

14.22 Adverse Event Monitoring

AEs will be recorded and reviewed at all scheduled and unscheduled study visits from the time the ICF is signed (Screening) through Week 24 (TOC). New AEs starting after Week 24 and until Week 36 will be recorded only if they led to the use of other antifungal medications or topical vaginal treatment, if they are a vaginal bacterial or parasitic infection, or if they are deemed related to the previously administered study drug. See Section 16.0 for further reference.

15.0 Study Schedule

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

Table 2: Schedule of Visits and Procedures (Study SCY-078-304)

	Screen[a]	Acute Phase (Days -14 to -1 [+3 d])			Prevention of Recurrence									
					Study Treatment Period (D1 to W24)							Follow-up Period (W25 to W36)		Unsch[c]
Study Week/Day **Study Procedures**	**D -16 to -14**	**D-14[a]**	**D -11 & -8 Phone**	**D -4 to -2 Lab**	**W1/ D1 (BL)**	**W4/ D28 (±3 d)**	**W8/ D56 (±3 d)**	**W12/ D84 (±3 d)**	**W16/D112 Phone[b]**	**W20/D140 Phone[b]**	**W24/ D168 (TOC) (±3 d)**	**W28 & W32 Phone[b]**	**W36 (EOFU) (±3 d)**	
Informed Consent	X													
Assignment of Subject ID number	X													
Inclusion/exclusion criteria	X				X									
Medical history and demographics	X													
Abbreviated physical exam	X				X			X			X			If needed
Urine pregnancy test	X				X									If needed
Vulvovaginal sample for KOH[d]	X					If PR[e]	If PR[e]	If PR[e]			If PR[e]		If PR[e]	If PR[e]
Vulvovaginal sample for fungal culture[d]	X				X	If PR[e]	If PR[e]	X			X		X	If PR[e]
Vulvovaginal sample for pH[d]	X				X	If PR[e]	If PR[e]	If PR[e]			If PR[e]		If PR[e]	If PR[e]
Vulvovaginal sample for other pathogens[d]	X					If PR[e]	If PR[e]	If PR[e]			If PR[e]		If PR[e]	If PR[e]
Vulvovaginal exam[f] and rating of signs by the investigator	X				X	If PR[e]	If PR[e]	X			X		If PR[e]	If PR[e]
Rating of vulvovaginal symptoms by the subject[g]	X	X----------X			X ----------X									X
Open-label FLU dispensing		X												
Open-label FLU dosing[h]		X	X											
Subject diary dispensing and collection		X			X			X			X		X	

	Screen[a]	Acute Phase (Days -14 to -1 [+3 d])			Prevention of Recurrence									
					Study Treatment Period (D1 to W24)							Follow-up Period (W25 to W36)		Unsch[c]
Study Week/Day **Study Procedures**	**D -16 to -14**	**D-14[a]**	**D -11 & -8 Phone**	**D -4 to -2 Lab**	**W1/ D1 (BL)**	**W4/ D28 (±3 d)**	**W8/ D56 (±3 d)**	**W12/ D84 (±3 d)**	**W16/D112 Phone[b]**	**W20/D140 Phone[b]**	**W24/ D168 (TOC) (±3 d)**	**W28 & W32 Phone[b]**	**W36 (EOFU) (±3 d)**	
Subject diary completion		X----------											X	
Subject diary review					X	X	X	X			X		X	X
Sample collection for safety labs (hematology and blood chemistry)				X[i]				X					X[j]	If needed
Open-label FLU collection and compliance evaluation					X									
Assessment of clinical outcome to FLU treatment					X[k]									
Randomization					X									
Blinded study drug dispensing					X			X						
Blinded study drug dosing[l]					X	X	X	X	X	X				
Quality-of-life assessment[m]		X			X			X			X		X	
Assessment for potential recurrence						X	X	X	X	X	X	X	X	X
Blinded study drug compliance evaluation						X	X	X	X	X	X			
Blinded study drug collection								X			X			
Vital Signs	X	X			X	X	X	X			X		X	X
Prior & concomitant medication review	X	X	X		X	X	X	X	X	X	X	X	X	X
Adverse event monitoring	X	X	X		X	X	X	X	X	X	X	X	X	X

Abbreviations: BL = Baseline; d = day; D = Day; EOFU = end of follow-up; FLU = fluconazole; ID = identification; KOH = potassium hydroxide; Phone = Phone contact; PR = potential recurrence; Screen = Screening; TOC = test of cure; Unsch = unscheduled; VSS = vulvovaginal signs and symptoms; VVC = vulvovaginal candidiasis; W = Week;

Note regarding visits: Whenever possible, on-site visits and phone contacts will be scheduled to occur on the date of dosing (or as close to the date of dosing as possible) to facilitate reminding subjects to take their study doses. This is applicable for the Baseline (Day 1), Week 4, Week 8, Week 12, Week 16 (phone contact), and Week 20 (phone contact) visits. Phone contacts will be conducted to check for adverse events, treatment compliance, potential recurrence, and concomitant medication use, including other antifungal agents.

	Screen[a]	Acute Phase (Days -14 to -1 [+3 d])			Prevention of Recurrence									
					Study Treatment Period (D1 to W24)							Follow-up Period (W25 to W36)		Unsch[c]
Study Week/Day **Study Procedures**	**D -16 to -14**	**D-14[a]**	**D -11 & -8 Phone**	**D -4 to -2 Lab**	**W1/ D1 (BL)**	**W4/ D28 (±3 d)**	**W8/ D56 (±3 d)**	**W12/ D84 (±3 d)**	**W16/D112 Phone[b]**	**W20/D140 Phone[b]**	**W24/ D168 (TOC) (±3 d)**	**W28 & W32 Phone[b]**	**W36 (EOFU) (±3 d)**	

a. Screening and Day-14 may occur on the same day.

b. If there is suspicion of a potential recurrence, subjects will be strongly discouraged from self-administering any treatment and will be instructed to visit the study center for a proper evaluation of their recurrence before initiating any VVC treatment.

c. Unscheduled visits should be conducted anytime that there are symptoms indicating a potential recurrence or an adverse event. If there is suspicion of a potential recurrence, subjects will be strongly discouraged from self-administering any treatment and will be instructed to visit the study center for a proper evaluation of their recurrence before initiating any VVC treatment.

d. Vulvovaginal specimens will be obtained at the specified visits and anytime that a recurrence is suspected for local vaginal pH determination and KOH testing as well as to rule out bacterial vaginosis and *Trichomonas vaginalis* (wet-mount or other, process locally). Testing for *Neisseria Gonorrhoeae, Chlamydia trachomatis* or *Herpes* virus may also be conducted if these pathogens are suspected (central laboratory). Samples for fungal culture should also be collected for processing at a central laboratory. Susceptibility testing will be done centrally at Screening and for all positive cultures during the study.

e. Only if there is suspicion of a potential recurrence.

f. If a subject is actively menstruating at an on-site study visit that requires a vaginal exam, the visit should be rescheduled as soon as the subject's period ends but in no case more than 7 days after the initially scheduled visit.

g. From Baseline (Day 1) through the Week 36 (EOFU) visit, subjects will rate their symptoms and record their scores on the VSS Scale included in their subject diaries. Symptoms of infection will be rated on a weekly basis and at the time of each scheduled or unscheduled visit to the site.

h. The first dose of fluconazole will be administered at the site on Day -14, after all other visit procedures have been done. The remaining doses will be self-administered by the subjects at home.

i. Conducted by the central lab. Results will be reviewed at Baseline (Day 1).

j. Only if needed to follow up on a lab abnormality

k. If the subject has a culture-confirmed *Candida* spp. infection from the sample collected at Screening, achieves a significant resolution of all signs and symptoms of infection (total composite score ≤ 2 on the VSS Scale) and meets other eligibility criteria for the study, she will enter the Prevention of Recurrence Phase. Subjects who fail treatment with open-label fluconazole in the Acute Phase but continue to meet all other eligibility criteria will enter the open-label ibrexafungerp Nested Sub-Study (see Section 21.3 [Appendix C]). Subjects who are not eligible for this study or the Nested Sub-Study will be discontinued.

l. Oral ibrexafungerp or placebo administered as a single-day treatment repeated every 4 weeks (28 days [±3]) for a total of 6 single-day treatments (Baseline [Day 1], Week 4, Week 8, Week 12, Week 16 and Week 20). Each single-day treatment will consist of two doses of ibrexafungerp 300 mg each or placebo given 12 (±4) hours apart. Subjects will continue study drug treatment regardless of recurrence and/or administration of antifungal therapy. The first dose will be administered at the study site (Baseline [Day 1]) and the remaining doses will be self-administered by the subjects at home. Study drug should be administered preferably with or

	Screen[a]	Acute Phase (Days -14 to -1 [+3 d])			Prevention of Recurrence									
					Study Treatment Period (D1 to W24)							Follow-up Period (W25 to W36)		Unsch[c]
Study Week/Day **Study Procedures**	**D -16 to -14**	**D-14[a]**	**D -11 & -8 Phone**	**D -4 to -2 Lab**	**W1/ D1 (BL)**	**W4/ D28 (±3 d)**	**W8/ D56 (±3 d)**	**W12/ D84 (±3 d)**	**W16/D112 Phone[b]**	**W20/D140 Phone[b]**	**W24/ D168 (TOC) (±3 d)**	**W28 & W32 Phone[b]**	**W36 (EOFU) (±3 d)**	

immediately after a meal.

m. Quality of Life tools will include: Euro Quol 5 Dimensions (EQ-5D), Short Form Health Survey (SF-36) and Female Sexual Distress-Revised Scale (FSDS)

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 (Day 1) 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 or accompanied by total bilirubin > 2 x ULN

16.4 Overdose

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

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

16.5 Pregnancy

Female subjects who become pregnant should be immediately discontinued from the study and followed up to determine the outcome of the pregnancy. The pregnancy must be reported to the Sponsor within 24 hours of the site becoming aware of the pregnancy using the pregnancy reporting form. 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. The pregnancy itself is not to be reported as an AE or SAE. 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 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 principal investigator (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.

16.8 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.

16.9 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.

16.10 Adverse Event Collection Timeframe

AEs and SAEs will be recorded from the time the ICF is signed (Screening) through Week 24 (TOC). New AEs starting after Week 24 and until Week 36 will be recorded only if they led to the use of other antifungal medications or topical vaginal treatment, or if they are a vaginal bacterial or parasitic infection, or if they are deemed related to the previously administered study drug.

All AEs reported by the subject or observed by members of the clinical staff will be evaluated by the 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.

16.11 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.

16.12 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).

16.13 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 PPD Safety Surveillance (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.

16.14 Procedures for Emergency Unblinding

This is a double-blind 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 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 Investigator's Brochure 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.

17.3 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 analysis 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 tabulated for incidence and categorical variables. For parameters measured over time, observed values and changes from baseline will be described for each time point.

The Mycologically Proven Recurrence and Mycological Eradication rates will be described by baseline *Candida* species, when the number of isolates per species allows.

The percentage of subjects with Mycologically Proven Recurrence will be described by number of VVC episodes in the 12 months prior to randomization.

All analyses will be presented by treatment group, as appropriate. 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 final statistical analyses in detail will be provided as a separate document. The SAP will be finalized prior to the unblinding of the study treatments for analysis.

18.1 Sample Size Determination

The primary endpoint of the study is the percentage of subjects with documented Clinical Success up to TOC (Week 24). Assuming response rates of 65% and 43% for ibrexafungerp and placebo, respectively; 90% power; and an alpha level of 0.05, approximately 240 subjects randomized at a 1:1 ratio are needed to declare a difference between ibrexafungerp and placebo at Week 24 based on Fisher's Exact test.

In order to be randomized, a subject should have achieved the proposed significant resolution of signs and symptoms (total composite score ≤2 on the VSS Scale) after receiving fluconazole therapy for an acute episode and have a positive culture for *Candida* spp. from the sample collected at Screening. It is estimated that approximately 320 subjects will need to enter the Acute Phase to provide 240 subjects randomized to the Prevention of Recurrence Phase. Enrollment into the Acute Phase will be discontinued when approximately 240 subjects have been randomized.

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 confirmed mycological culture for yeast at Screening and a negative culture for yeast at Baseline (Day 1).
- **Per-Protocol (PP) Population:** All ITT subjects who did not have major protocol deviations likely to affect study efficacy and who have available data at the TOC visit. Note that subjects who discontinue due to a study-drug-related AE will be classified as failures for the analyses of efficacy under the PP population.
- **Safety Population:** All randomized subjects who received at least one dose of study drug (ibrexafungerp or placebo) and who have at least one post-Baseline (Day 1) 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 (Week 24) assessment will be assigned as treatment failures. For subjects who withdraw from the study early, every effort will be made to collect TOC or EOFU visit information (as applicable) at the point of withdrawal. Missing data will be further described in the SAP for early withdrawal subjects.

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 EOFU 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

Efficacy assessments will be based on clinical evaluations, mycological testing and QOL.

The **primary efficacy endpoint** of the study is the percentage of subjects with documented Clinical Success (defined as subjects having a TOC evaluation and no Mycologically Proven, Presumed or Suspected Recurrence of VVC) up to TOC (Week 24). The **key secondary efficacy endpoint** is the percentage of subjects with no Mycologically Proven Recurrence (defined as an episode of VVC with a total composite score ≥ 3 on the VSS Scale and a culture positive for *Candida* spp. that required antifungal treatment) at TOC (Week 24).

Other secondary efficacy endpoints will also be assessed (see Section 9.3).

The following efficacy outcomes will be evaluated in the study:

- **Clinical Success:** Subjects having a TOC evaluation and no Mycologically Proven, Presumed or Suspected Recurrence of VVC
- **Recurrence of VVC**: In this study, Recurrences of VVC will be broken into three categories:
    - **Mycologically Proven Recurrence:** An episode of VVC with a total composite score ≥ 3 on the VSS Scale and a culture positive for *Candida* spp. that required antifungal treatment.
    - **Presumed Recurrence:** An episode of VVC with a total composite score ≥ 3 on the VSS Scale that required antifungal treatment and for which there is a positive KOH microscopy but no positive fungal culture.
    - **Suspected Recurrence**: An episode of VVC that required treatment with an antifungal agent (including self-administration with over-the-counter antifungals) regardless of VSS composite score but for which there is no mycological evidence of disease, such as a positive KOH microscopy or fungal culture.
- **Mycological Eradication:** Negative fungal culture (no growth of *Candida* species).

18.6.2 Efficacy Analyses

The efficacy analyses will be conducted using the ITT (primary analysis population), mITT, and PP populations. The efficacy parameters will be evaluated comparing the ibrexafungerp treatment group versus the placebo group.

The primary endpoint, the percentage of subjects with documented Clinical Success up to TOC (Week 24), will be analyzed using a Cochran-Mantel-Haenszel (CMH) test adjusted for site; p-values and 95% confidence intervals will be presented. Subjects whose results are missing at TOC (Week 24) will be imputed as failures in the analysis. In the event that model convergence is an issue with a stratified analysis, alternative

methods for accounting for site, or an unstratified analysis will be considered. A sensitivity analysis will be performed on the ITT population where subjects with missing values will be removed from the analysis.

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.

For the ordered categorical endpoint, a proportional odds model will be fitted accounting for the effects of treatment and site. The proportional odds model will fit an ordered regression model for the ordinal dependent variable as described by McCullagh (1980). If the assumption of proportional odds is violated alternative analyses will be considered which require a weaker assumption.

18.7 Safety

18.7.1 Safety Assessments

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

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

18.7.2 Analyses

No formal statistical analysis is planned for the safety data. 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.

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

18.8 Interim Analyses

No interim analyses are planned for this study.

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 United States 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 GCP 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. Additional local regulatory requirements may be applicable for participation of subjects below the age of consent. 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. or other yeast isolates (see Section 14.7) 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. Sobel JD. Recurrent vulvovaginal candidiasis. Am J Obstet Gynecol. 2016 Jan;214(1):15-21.
5. Sobel JD. Management of recurrent vulvovaginal candidiasis: unresolved issues. Curr Infect Dis Rep. 2006 Nov;8(6):481-6.
6. Sobel JD, Wiesenfeld HC, Martens M, Danna P, Hooton TM, Rompalo A, Sperling M, Livengood C 3rd, Horowitz B, Von Thron J, Edwards L, Panzer H, Chu TC. Maintenance fluconazole therapy for recurrent vulvovaginal candidiasis. N Engl J Med. 2004 Aug 26;351(9):876-83.
7. 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.

21.0 Appendices

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

21.1.1 Prohibited Medications

Other Investigational Drugs

No investigational drugs other than the study drug are allowed within 30 days before Screening and throughout the study.

Topical Vaginal Corticoids and Contraceptives

No topical vaginal corticoids and topical vaginal contraceptives are allowed during the study. Topical vaginal corticosteroids are prohibited from 7 days prior to the Screening visit to the Week 24 (TOC) visit. Subjects must refrain from using any topical vaginal contraceptives such as spermicides or intra-vaginal hormonal contraceptive devices such as vaginal rings as these may interfere with the efficacy evaluations.

Other Systemic or Topical Vaginal Antifungals

No systemic or topical vaginal antifungal treatment other than the study drug, including prescription or over-the-counter products, is allowed from 28 days prior to Day -14 and throughout the study unless used as rescue medication.

CYP3A4/5 Inhibitors and Inducers

The medications listed below are also prohibited:

Strong CYP3A4/5 inhibitors and CYP3A4/5 inducers

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

a. The CYP3A4/5 inhibitors listed in this table are not permitted during the 48 hours prior to enrollment and during study treatment.
b. The CYP3A4/5 inducers listed in this table are not permitted during the 14 days prior to enrollment and during study treatment.

P-glycoprotein (P-gp) substrates

P-gp Drug Substrates[a]
digoxin, colchicine, quinidine, vinblastine, talinolol, methotrexate, rifampin, dabigatran, fexofenadine

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

21.1.2 Medications to be administered with Caution and Monitored as Appropriate

CYP3A4 substrates

CYP	Substrates
3A4	*In vitro*, ibrexafungerp 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 with drugs known to be CYP3A sensitive substrates with narrow therapeutic index, such as midazolam. Subjects receiving sirolimus, tacrolimus, warfarin, cyclosporine or amiodarone are permitted for enrollment in the study and these medications may be administered concomitantly with ibrexafungerp 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 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 with drugs known to be OATP1B3 selective substrates. Therefore, caution should be exercised when administering ibrexafungerp 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

21.2 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

21.3 Appendix C: Protocol for Study SCY-078-304S

Study Title: An exploratory, open-label, single-group ibrexafungerp sub-study to evaluate the efficacy and safety of oral ibrexafungerp in the treatment of acute VVC in patients with recurrent VVC that has not responded to oral fluconazole treatment

This study is an exploratory, open-label, single-group sub-study to evaluate the efficacy and safety of oral ibrexafungerp (SCY-078) in the treatment of subjects with acute VVC who did not respond to oral fluconazole treatment. Subjects with a history of recurrent VVC (enrolled in the Main Study [Study SCY-078-304] with an acute VVC episode), who had a culture-confirmed VVC at Screening (Main Study) and failed to meet resolution of their vulvovaginal signs and symptoms after fluconazole treatment (as defined in the SCY-078-304 study protocol) will be eligible for this sub-study (SCY-078-304S). These subjects will not be eligible for randomization into the Prevention of Recurrence Phase of the Main Study but will be offered open-label, one-day oral ibrexafungerp treatment for their unresolved VVC episode under this sub-study.

The full study protocol for study SCY-078-304 is provided from Section 5.0 onwards. This Appendix C describes the protocol for this Nested Sub-Study (SCY-078-304S) and all references to "the study" in this appendix refer to this study SCY-078-304S, unless otherwise noted.

21.3.1 Protocol Synopsis

Title: An exploratory, open-label, single-group ibrexafungerp sub-study to evaluate the efficacy and safety of oral ibrexafungerp in the treatment of acute vulvovaginal candidiasis in patients with recurrent VVC that has not responded to oral fluconazole treatment
STUDY OBJECTIVES: **Primary Objective:** • To evaluate the efficacy of a single-day dosing of oral ibrexafungerp in subjects with a history of RVVC who failed oral fluconazole therapy for the treatment of an acute VVC episode, based on Clinical Success. **Secondary Objectives:** • To evaluate the efficacy of a single-day dosing of oral ibrexafungerp in subjects with a history of RVVC who failed oral fluconazole therapy for the treatment of an acute VVC episode, based on mycological and clinical outcomes. • To evaluate the safety and tolerability of a single-day dosing of oral ibrexafungerp in subjects with a history of RVVC who failed oral fluconazole therapy for the treatment of an acute VVC episode.
STUDY ENDPOINTS: **Primary Endpoint:** • Efficacy as measured by the percentage of subjects with Clinical Success (at least 50% reduction from Baseline in the total composite VSS score with no additional antifungal therapy required based on investigator's judgment) at the Test-of-Cure (TOC) visit.

Secondary Endpoints:

Efficacy as measured by:

- The percentage of subjects with Clinical Improvement (partial or complete resolution of signs and symptoms [total composite score ≤1 on the VSS Scale] with no additional antifungal therapy required based on investigator's judgment) at the TOC visit.
- The percentage of subjects with Clinical Cure (complete resolution of signs and symptoms [total composite score of 0 on the VSS Scale] with no additional antifungal therapy required based on investigator's judgment) at the TOC visit.
- The percentage of subjects with Mycological Eradication (negative culture for growth of *Candida* spp.) at the TOC visit.
- The percentage of subjects with both Clinical Cure and Mycological Eradication at the TOC visit.
- The percentage of subjects with Continued Clinical Success (sustained resolution of signs and symptoms in subjects who achieved Clinical Success at the TOC visit) at the FU visit.
- The absolute change in total composite VSS score from Baseline to the TOC and FU visits.

Safety and tolerability as measured by:

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

STUDY DESIGN:

This study is an exploratory, open-label, single-group nested sub-study to evaluate the efficacy and safety of oral ibrexafungerp (SCY-078) in the treatment of subjects with acute VVC who did not respond to oral fluconazole treatment. Subjects with a history of recurrent VVC (enrolled in the Main Study [study SCY 078 304] with an acute VVC episode), who had a culture-confirmed VVC at Screening (Main Study) and failed oral fluconazole will be eligible for this sub-study (SCY-078-304S). A subject will be considered to have failed oral fluconazole therapy if she did not achieve a significant resolution of the signs and symptoms of infection (defined as a total composite score ≤ 2 on the VSS Scale) at the Baseline Visit (Day 1) following treatment with oral fluconazole 150 mg once daily (QD) on Days -14, -11 and -8. Eligible subjects must continue to meet all other applicable eligibility criteria of the Main Study (study SCY-078-304) to enter this study. Subjects who are eligible for this study will be offered open-label, one-day oral ibrexafungerp treatment for their unresolved VVC episode.

Approximately 60 subjects are planned to enter the study. All eligible subjects will receive oral ibrexafungerp administered as a single-day treatment consisting of two 300-mg doses (total dose = 600 mg) given 12 hours apart (±4 hours).

The study will consist of the following visits:

- **Baseline visit (Day 1):** Subjects who meet all criteria for this study will receive the first dose of study drug, oral ibrexafungerp 300 mg, at the site and will self-administer the second 300-mg dose at home, 12 hours (±4 hours) after the first dose. At this visit, subjects will be provided with subject diaries to record the date and time of their second study drug dose and to rate their vulvovaginal symptoms of infection, AEs and concomitant medication use from the Baseline (Day 1) visit until the TOC visit (Day 11 ± 3).
- **TOC visit (Day 11 [±3]):** At this visit, treatment compliance will be evaluated, and 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 standardized, predefined scale [see STUDY EVALUATIONS below]).

  If the baseline vulvovaginal signs and symptoms have not improved or have worsened, vulvovaginal samples for fungal culture, species identification and antifungal susceptibility testing will be obtained and sent to a designated central laboratory. Additional vaginal

samples will be obtained for a potassium hydroxide (KOH) testing by the local laboratory if symptoms persist or have worsened. An abbreviated physical exam, vital signs measurements and safety laboratory tests will also be performed.

- **FU visit (Day 25 [±4]):** At the FU visit, subjects will rate their symptoms of infection on the VSS Scale. Vulvovaginal samples for pH determination, KOH testing and fungal culture should be obtained if there is persistence or worsening of vulvovaginal symptoms. Only if symptoms are present, the investigator will perform a vulvovaginal examination to rate the subject's signs of infection.

The study will include efficacy, safety and tolerability assessments. Efficacy assessments will be based on clinical evaluations (rating of signs and symptoms of infection) and mycological testing (direct microscopic examinations and fungal cultures). Safety and tolerability will be evaluated by AEs, vital signs, safety laboratory tests and study treatment discontinuations. See STUDY EVALUATIONS for further details.

TARGET POPULATION: The study population will include female subjects 12 years and older with RVVC.

INCLUSION CRITERIA:

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

1. Subject meets the following criteria at Baseline (Day 1):
   a) Failure to achieve a significant resolution of the signs and symptoms of the *Candida* infection (total composite score ≥ 3 on the VSS Scale).
   b) Culture positive for *Candida* spp. in a vaginal sample collected at Screening (Main Study).
   c) Normal vaginal pH (≤ 4.5)
2. Subject meets all other inclusion criteria in Section 11.1 of the Main Study (except Inclusion Criterion No. 3a, requiring a total composite score ≤ 2 on the VSS Scale).

EXCLUSION CRITERIA:

A subject will be excluded from participation in this study if she meets any of the exclusion criteria listed in Section 11.2 of the Main Study.

STUDY DRUGS:

The study drug administered during the study will be provided by the Sponsor and will consist of oral ibrexafungerp (150-mg tablets). The study drug will be supplied as ibrexafungerp citrate drug product, a tablet containing 150 mg of ibrexafungerp active ingredient on a free-base basis for oral administration. In addition to the active ingredient, the tablet formulation also contains silicified microcrystalline cellulose, crospovidone, mannitol, colloidal silicon dioxide, magnesium stearate (non-bovine) and butylated hydroxyanisole.

STUDY TREATMENT GROUPS:

This is an open-label, single-group study. All subjects will receive oral ibrexafungerp administered as a single-day treatment (Baseline [Day 1]) consisting of two 300-mg doses (total dose = 600 mg) given 12 hours apart (±4 hours). The study drug should be administered preferably with or immediately after a meal.

STUDY BLINDING, RANDOMIZATION AND STRATIFICATION: This is an open-label, single-group study. There will be no study-drug blinding, randomization or stratification.

STUDY EVALUATIONS

Efficacy Evaluations

Clinical Evaluation: The signs (edema, erythema and excoriation or fissures) and symptoms (itching, burning and irritation) of infection will be assessed by the investigator and the subject, respectively, on the VSS Scale. 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 Evaluations: Mycological tests will include direct wet mount microscopic examination (performed locally) to visualize clue cells indicative of bacterial vaginosis or trichomonas, direct microscopic examination with 10% KOH (performed locally) to identify yeast, and fungal cultures (performed at the central lab) for species identification and susceptibility testing.

Safety and Tolerability Assessments

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

STATISTICAL ANALYSES:

Sample Size Determination

The primary endpoint of the study is the percentage of subjects with Clinical Success (at least 50% reduction from Baseline in the total composite VSS score with no additional antifungal therapy required based on investigator's judgment) at the TOC visit. As this is a single arm sub-study, a statement regarding the Clinical Success rate and 95% confidence interval will be produced. It is estimated that 60 subjects will be included based upon published fluconazole failure rates. With a study of this size, if the Clinical Success rate for ibrexafungerp were 50%, this would correspond to a 95% confidence interval spanning from 36.8% to 63.2%. Given it is expected that the Clinical Success for ibrexafungerp in subjects who have already failed fluconazole will be low as these subjects had already failed to respond, a sub-study of this size is appropriate to assess the efficacy of ibrexafungerp in this patient population

Analysis Populations

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

- **Intent-to-Treat (ITT) Population**: All ibrexafungerp-treated subjects.
- **Modified Intent-to-Treat (mITT) Population:** All treated subjects who have a positive culture for *Candida* species at Baseline.
- **Safety Population:** All randomized subjects who received at least one dose of study drug and who have at least one post-Baseline evaluation.

Efficacy Analysis

Efficacy assessments will be based on clinical evaluations, mycological testing and additional antifungal use.

The primary efficacy endpoint, the percentage of subjects with Clinical Success (at least 50% reduction from Baseline in the total composite VSS score with no additional antifungal therapy required based on investigator's judgment) at TOC will be assessed on the mITT population and will present the Clinical Success rate and the 95% confidence interval calculated using the method of Clopper and Pearson. Missing data for the primary endpoint will be imputed as failure. In addition, the Clinical Success rate and 95% CI will be calculated where subjects with missing values will be removed from the analysis. All other efficacy data will be summarized, but not subject to formal statistical analysis.

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

Clinical Outcomes

- Clinical Success: at least 50% reduction from Baseline in the total composite VSS score with no additional antifungal therapy required based on investigator's judgment
- Clinical Improvement: partial or complete resolution of signs and symptoms (total composite score ≤1 on the VSS Scale) with no additional antifungal therapy required based on investigator's judgment
- Clinical Cure: complete resolution of signs and symptoms (total composite score of 0 on the VSS Scale) with no additional antifungal therapy required based on investigator's judgment
- Continued Clinical Success: sustained resolution of signs and symptoms in subjects who achieved Clinical Success at the TOC visit
- Clinical Failure: Persistence and/or worsening of signs and symptoms or need for additional antifungal therapy

Mycological Outcomes

- Mycological Eradication: negative culture for growth of *Candida* species.
- Mycological Persistence: positive culture for growth of *Candida* species.

Safety Analysis

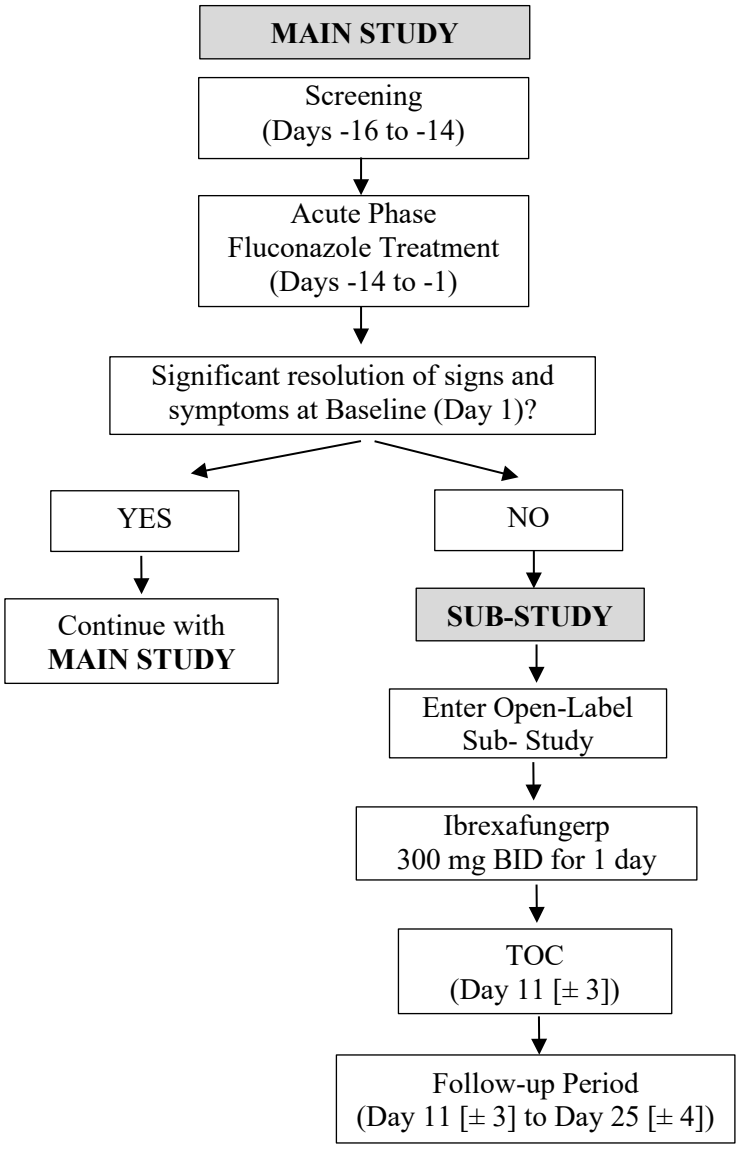
Safety will be evaluated throughout the study, including the following parameters: AEs, treatment discontinuations, physical examination, vital signs, safety laboratory tests, and prior and concomitant medications.

No formal statistical analysis is planned for the safety data. Safety presentations 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.

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 for laboratory tests.

21.3.2 Schematic of Study Design



Abbreviations: BID = twice a day; TOC = Test of Cure
***Note: See Section 5.0 for Main Study details.**

21.3.3 Background Information and Scientific Rationale

Background information for VVC, recurrent VVC (RVVC) and ibrexafungerp is available in Section 7.1 of the Main Study (study SCY-078-304).

Considering the properties of ibrexafungerp as a potent antifungal compound with fungicidal activity against *Candida* spp., enhanced activity in low pH, concentration in vaginal tissue and spectrum of activity encompassing fluconazole-resistant strains, if ibrexafungerp is proven effective, it will represent an important alternative treatment for subjects suffering from VVC.

In order to evaluate the efficacy of ibrexafungerp in the treatment of VVC that is not responding to oral fluconazole treatment, subjects who fail to respond to fluconazole treatment given as 150 mg once a day on Days -14, -11 and -8, for a total of 3 doses in the Acute Phase of the Main Study (study SCY-078-304) will be entered into this study.

A subject will be considered not to respond to oral fluconazole treatment if she had a culture-confirmed vulvovaginal *Candida* spp. infection at Screening (Main Study) but did not achieve a significant resolution of her signs and symptoms at Baseline (Day 1). In addition, subjects must continue to meet all other eligibility criteria for the Main Study to enter this study (see Section 21.3.7).

Subjects will receive oral ibrexafungerp 300 mg twice a day (BID) for one day (i.e., ibrexafungerp administered as a single-day treatment consisting of two doses of 300 mg each [given 12 hours apart]) on Day 1 only (total dose = 600 mg).

The ibrexafungerp selected dose of 300 mg BID for 1day 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 and is the dose in ongoing Phase 3 studies in the treatment of acute VVC.

The primary endpoint of the study is the percentage of subjects with Clinical Success (defined as at least 50% reduction from Baseline in the total composite Vulvovaginal Signs and Symptoms [VSS] score, with no additional antifungal therapy required based on investigator's judgment) at the Test-of-Cure (TOC) visit. Secondary endpoints will include the percentage of subjects with Clinical Improvement (partial or complete resolution of signs and symptoms [total composite score ≤1 on the VSS Scale] with no additional antifungal therapy required based on investigator's judgment), Clinical Cure (complete resolution of signs and symptoms [total composite score of 0 on the VSS Scale] with no additional antifungal therapy required based on investigator's judgment), Mycological Eradication, and both Clinical Cure and Mycological Eradication at the TOC visit. The percentage of subjects with Continued Clinical Success (sustained resolution of signs and symptoms in subjects who achieved Clinical Success at the TOC visit) at the Follow-up (FU) visit, and the absolute change in total composite VSS score from Baseline to the TOC and FU visits will also be assessed as secondary endpoints. These endpoints are considered appropriate for this study population and design.

21.3.4 Study Objectives

21.3.4.1 Primary Objective

- To evaluate the efficacy of a single-day dosing of oral ibrexafungerp in subjects with a history of RVVC who failed oral fluconazole therapy for the treatment of an acute VVC episode, based on Clinical Success.

21.3.4.2 Secondary Objectives

- To evaluate the efficacy of a single-day dosing of oral ibrexafungerp in subjects with a history of RVVC who failed oral fluconazole therapy for the treatment of an acute VVC episode, based on mycological and clinical outcomes.
- To evaluate the safety and tolerability of a single-day dosing of oral ibrexafungerp in subjects with a history of RVVC who failed oral fluconazole therapy for the treatment of an acute VVC episode.

21.3.5 Study Endpoints

21.3.5.1 Primary Endpoint

Efficacy as measured by:

- The percentage of subjects with Clinical Success (at least 50% reduction from Baseline in the total composite VSS score with no additional antifungal therapy required based on investigator's judgment) at the Test-of-Cure (TOC) visit.

21.3.5.2 Secondary Endpoints

Efficacy as measured by:

- The percentage of subjects with Clinical Improvement (partial or complete resolution of signs and symptoms [total composite score $\leq$1 on the VSS Scale] with no additional antifungal therapy required based on investigator's judgment) at the TOC visit.
- The percentage of subjects with Clinical Cure (complete resolution of signs and symptoms [total composite score of 0 on the VSS Scale] with no additional antifungal therapy required based on investigator's judgment) at the TOC visit.
- The percentage of subjects with Mycological Eradication (negative culture for growth of *Candida* spp.) at the TOC visit.
- The percentage of subjects with both Clinical Cure and Mycological Eradication at the TOC visit.
- The percentage of subjects with Continued Clinical Success (sustained resolution of signs and symptoms in subjects who achieved Clinical Success at the TOC visit) at the FU visit.

- The absolute change in total composite VSS score from Baseline to the TOC and FU visits.

Safety and tolerability as measured by:

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

21.3.6 Study Design

This Nested Sub-Study is an exploratory, open-label, single-group study to evaluate the efficacy and safety of oral ibrexafungerp in the treatment of acute episodes of VVC in subjects with a history of RVVC who have not responded to 3 doses of oral fluconazole treatment.

A subject will be considered to have failed oral fluconazole therapy if she had a positive culture for *Candida* spp. at Screening (Main Study) but did not achieve a significant resolution of the signs and symptoms of infection (defined as a total composite score ≤ 2 on the VSS Scale) at the Baseline Visit (Day 1) following treatment with oral fluconazole 150 mg once daily (QD) on Days -14, -11 and -8. Eligible subjects must continue to meet all other applicable eligibility criteria of the Main Study (study SCY-078-304) to enter this study.

Approximately 60 subjects are planned to enter this study. All eligible subjects will receive oral ibrexafungerp administered as a single-day treatment consisting of two 300-mg doses (total dose = 600 mg) given 12 hours apart (±4 hours).

The study will consist of the following visits:

- Baseline visit (Day 1): Single-day, open-label administration of two doses of oral ibrexafungerp 300 mg
- TOC visit (Day 11 [±3]): Assessment of efficacy and safety
- FU visit (Day 25 [±4])

The study will include efficacy, safety and tolerability assessments.

21.3.6.1 Study Visits

Baseline Visit (Day 1): Study Drug Dosing

Subjects who meet all criteria for this study will receive the first dose of study drug, oral ibrexafungerp 300 mg, at the site and will self-administer the second 300-mg dose at home, 12 hours (±4 hours) after the first dose. At this visit, subjects will be provided with subject diaries to record the date and time of their second study drug dose and to rate their vulvovaginal symptoms of infection, AEs and concomitant medication use from the Baseline (Day 1) visit until the TOC visit (Day 11 ± 3).

TOC Visit (Day 11 [± 3]): Assessment of Efficacy

At the TOC visit (Day 11), treatment compliance will be evaluated, and 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 (see Section 21.2 [Appendix B] of the Main Study).

If the baseline vulvovaginal signs and symptoms have not improved or have worsened, vulvovaginal samples for fungal culture, species identification and antifungal susceptibility testing will be obtained and sent to a designated central laboratory. Additional vaginal samples will be obtained for a potassium hydroxide (KOH) testing by the local laboratory if symptoms persist or have worsened. An abbreviated physical exam, vital signs measurements and safety laboratory tests will also be performed.

Follow-Up (Day 25 [± 4])

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

Unscheduled Visits

Unscheduled visits should be conducted anytime that there is indication of persistence or worsening of symptoms or an adverse event. If there is suspicion of persistence or worsening of symptoms, subjects will be strongly discouraged from self-administering any treatment and will be instructed to visit the study center for a proper evaluation before initiating any new VVC treatment.

All visits

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

21.3.6.2 Study Assessments

Efficacy Assessments

Efficacy assessments will be based on clinical evaluations (rating of signs and symptoms of infection) and mycological testing (direct microscopic examinations and fungal cultures).

- Clinical Evaluations: The signs (edema, erythema and excoriation or fissures) and symptoms (itching, burning and irritation) of infection will be assessed and rated by the investigator and the subject, respectively, on the VSS Scale (provided in Section 21.2 [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 VSS score.

- Mycological Evaluations: Mycological tests will include direct wet mount microscopic examination (performed locally) to visualize clue cells indicative of bacterial vaginosis or trichomonas, direct microscopic examination with 10% KOH (performed locally) to identify yeast and fungal cultures (performed at the central lab) for species identification and susceptibility testing.

Safety and Tolerability Assessments

Safety and tolerability will be evaluated by AEs, vital signs, safety laboratory tests and study treatment discontinuations.

A detailed description of study procedures is available in Section 21.3.10.

21.3.7 Study Population

The population will include subjects enrolled in the Main Study who fail oral fluconazole treatment for their VVC episode.

21.3.7.1 Inclusion Criteria

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

1. Subject meets the following criteria at Baseline (Day 1):
   a. Failure to achieve a significant resolution of the signs and symptoms of the *Candida* infection (total composite score ≥ 3 on the VSS Scale).
   b. Culture positive for *Candida* spp. in a vaginal sample collected at Screening (Main Study).
   c. Normal vaginal pH (≤ 4.5)
2. Subject meets all other inclusion criteria in Section 11.1 of the Main Study (except Inclusion Criterion No. 3a, requiring a total composite score ≤ 2 on the VSS Scale).

21.3.7.2 Exclusion Criteria

A subject will be excluded from participation in this study if she meets any of the exclusion criteria listed in Section 11.2 of the Main Study.

21.3.7.3 Discontinuation Criteria

A subject may me be discontinued from this study for any of the following reasons:

- Withdrawal of consent by the subject and/or subject's legal guardian;
- 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).

If the subject withdraws consent on or before the TOC (Day 11) visit, all TOC visit procedures should be performed at the early termination visit. If the subject withdraws consent on or before the FU (Day 25) visit, all FU visit procedures should be performed at the early termination visit. Once the subject has completed all assessments for the early termination visit, as appropriate, no further follow-up will be needed unless there is an ongoing study drug-related AE. All study drug-related AEs should be followed up until resolution.

21.3.8 Study Treatments

21.3.8.1 Study Treatment Groups

This is an open-label, single-group study. All subjects will receive oral ibrexafungerp administered as a single-day treatment (Baseline [Day 1]) consisting of two 300-mg doses (total dose = 600 mg) given 12 hours apart (±4 hours). The study drug should be administered preferably with or immediately after a meal.

21.3.8.2 Study Drug Description, Formulation, Packaging, Labelling and Storage

The study drug administered during the study will be provided by the Sponsor and will consist of oral ibrexafungerp (150-mg tablets). The study drug will be supplied as ibrexafungerp citrate drug product, a tablet containing 150 mg of ibrexafungerp active ingredient on a free-base basis for oral administration. 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 pharmacist or appropriate designee at each clinical research site will be responsible for the study drug. For long-term storage at the site, ibrexafungerp must be kept in a secure, limited-access storage area (e.g., locked cabinet) and stored at room temperature.

Drug Accountability

The investigator or designee will inventory and acknowledge receipt of all shipments of the study drug during the Sub-Study. 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. After 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.

The study drug supplied for this study is only for use in subjects properly consented and enrolled under this protocol. 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 (Day 11) visit
- 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

21.3.8.3 Subject Compliance with Study Drug Dosing

Subjects (or subject's parent/legal representative, if applicable) will be instructed to have the assigned bottle of study medication (including empty containers) with them at the TOC (Day 11) visit. 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 their second study drug dosing. Details of treatment including any missed second 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 their second dose due to AEs related with tolerability.

21.3.9 Non-Study Treatments

21.3.9.1 Prior and Concomitant Medications

All medications (including prescription and over-the-counter medications, supplements, and herbal products) taken from Baseline (Day 1) through the TOC (Day 11) visit will be recorded on the eCRF. Only the use of other antifungal medications, medications used to treat vaginal bacterial or parasitic infections, topical vaginal medications or medications to treat a study-drug related AE will be recorded after the TOC (Day 11) visit through the last study visit (FU [Day 25] visit). Start and stop dates of concomitant medications will be recorded on the eCRF. Prior and concomitant medications will be reviewed and recorded at all scheduled and unscheduled study visits.

21.3.9.2 Prohibited Medications and Medications to be Administered with Caution

Certain medications are not permitted during the study or must be administered with caution. See Section 21.1 (Appendix A) of the Main Study for details.

21.3.10 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 Sub-Study Table 1.

Study days are counted relative to the first dose of study drug (Baseline [Day 1]). If a subject is actively menstruating at a study visit that requires a vaginal exam, the visit should be rescheduled as soon as the subject's period ends but in no case more than 7 days after the initially scheduled visit. Unscheduled visits will be conducted any time that there is persistence or worsening of symptoms.

21.3.10.1 Informed Consent

At the Screening visit of the Main Study, subjects (or their legal representative, if applicable) will provide consent for participation in both the Main Study and this study, and will enter either study based on the criteria met at Baseline (Day 1) (see Section 11.1 and Section 11.2 in the Main Study).

21.3.10.2 Assignment of Subject Number

Subjects included in the study will maintain the same unique subject identification (ID) number provided at the Screening visit of the Main Study, except that an additional letter coding will be added to the ID number to identify subjects participating in this study.

21.3.10.3 Inclusion/Exclusion Criteria

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

21.3.10.4 Abbreviated Physical Exam

An abbreviated physical examination, including general appearance and an overall examination of body systems, will be conducted at the Baseline (Day 1) visit, the TOC (Day 11) visit and any unscheduled visit, if needed.

21.3.10.5 Urine Pregnancy Test

A urine pregnancy test based on the measurement of human chorionic gonadotropin with a sensitivity of at least 25 mIU/mL will be performed at the Baseline (Day 1) visit and at unscheduled visits, if needed, by the local laboratory for all subjects of childbearing potential. The subject must have a negative pregnancy test before taking the first dose of study drug.

21.3.10.6 Vulvovaginal Samples

The following vulvovaginal samples will be collected during the study:

- **Sample for direct microscopic examination with 10% KOH:** A vulvovaginal sample for KOH testing by the local laboratory will be obtained for all subjects at

the Baseline (Day 1) visit. If the Baseline (Day 1) vulvovaginal signs and symptoms have not improved or have worsened at the TOC (Day 11) and FU (Day 25) visits, a vaginal sample should be obtained for KOH testing by the local laboratory. Vaginal samples for KOH should also be collected any other time that a subject experiences persistence or worsening of symptoms (i.e., at unscheduled visits, if needed). The sample will be assessed by a local laboratory or at the site by the investigator or a qualified designee.

The direct microscopic examination with KOH is intended for the visualization of yeasts. If the KOH test is negative, the investigator should consider other causes for the persistence or worsening of the symptoms.

- **Sample for fungal culture**: A fungal culture will be collected at the Baseline (Day 1) visit for all subjects. If the Baseline (Day 1) vulvovaginal signs and symptoms have not improved or have worsened at the TOC (Day 11) and FU (Day 25) visits, a vaginal sample should be obtained for fungal culture. Vaginal samples for culture should also be collected any other time that a subject experiences persistence or worsening of symptoms (i.e., at unscheduled visits, if needed). The sample will be processed by a central laboratory for species identification. Positive cultures will also be tested for susceptibility against ibrexafungerp, fluconazole and additional antifungal agents, as deemed appropriate based on validated methods..
- **Sample for vaginal pH:** To be collected at the Baseline (Day 1) visit for all subjects and at the TOC (Day 11) and FU (Day 25) visits if vulvovaginal signs and symptoms have not improved or have worsened. Samples for pH should also be obtained any time that a subject experiences persistence or worsening of symptoms (i.e., unscheduled visits if needed). The sample will be assessed at the site by the investigator or a qualified designee.
- **Sample for identification of other pathogens:**
  - Samples (e.g. wet mount) to rule out bacterial vaginosis and *Trichomonas vaginalis* will be collected at Baseline (Day 1) and any time that a subject experiences persistence or worsening of symptoms. Samples will be assessed by a local laboratory or at the site by the investigator or a qualified designee.
  - Samples to rule out *Neisseria Gonorrhoeae, Chlamydia trachomatis* or *Herpes* virus are to be collected at the Baseline (Day 1) visit, and then at the TOC (Day 11) and FU (Day 25) visits if vulvovaginal signs and symptoms have not improved or have worsened. Samples should also be collected any time that there is persistence or worsening of symptoms if any of these pathogens is suspected. Samples will be processed by a central laboratory.

Procedures for collecting and processing local samples, as well as for shipping central laboratory vulvovaginal samples, will be described in the laboratory manual.

21.3.10.7 Vulvovaginal Examination and 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 Baseline (Day 1) and TOC (Day 11) visits. The vulvovaginal examination will be repeated at the FU (Day 25) 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 of symptoms, a vaginal examination with rating of signs by the investigator should be completed.

Investigators will assess the signs of infection using the VSS Scale provided in Section 21.2 (Appendix B) of the Main Study, 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.

If a subject is actively menstruating at the time of a study visit that requires a vulvovaginal exam, the visit should be rescheduled as soon as the subject's period ends but in no case more than 7 days after the initially scheduled visit.

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

Subjects will be asked to rate their vulvovaginal symptoms from Baseline (Day 1) through the TOC (Day 11) visit and at the FU (Day 25) visit. Subjects will also assess their symptom at unscheduled visits, as needed.

If the subject experiences persistence or worsening of symptoms, a vaginal examination with rating of signs by the investigator should be completed.

Subjects will rate their symptoms of infection using the VSS Scale (see Section 21.2 [Appendix B] of the Main Study), 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.

21.3.10.9 Single-Day Study Drug Dosing and Dispensing

At the Baseline (Day 1) visit, subjects will receive their first dose of study drug (ibrexafungerp 300 mg) at the site and will be given study drug to self-administer their second dose (ibrexafungerp 300 mg) at home, approximately 12 hours later on the same day. The two doses should be administered approximately 12 (±4) hours apart. Study drug should be administered preferably with or immediately after a meal.

21.3.10.10 Dispensing, Completion, Collection and Review of Subject Diaries

Subject diaries will be provided to all subjects at the Baseline (Day 1) visit for them to complete on a daily basis until the TOC (Day 11) visit. The subject diaries will include the VSS Scale so that subjects can rate their vulvovaginal symptoms (see Section 21.3.10.7 and Section 21.3.10.8 for sign and symptom rating procedures, respectively, and Section 21.2 [Appendix B] for the full VSS Scale). Subjects will also record other medical concerns or complaints, concomitant medications used, adverse events and second dose of study drug details. Subjects will be instructed to return their subject diaries at the TOC (Day 11) visit, when they will be collected and reviewed.

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 reviewed by the site and relevant findings included in the corresponding eCRFs modules (e.g. concomitant medications, AEs, etc.).

21.3.10.11 Study Drug Collection and Treatment Compliance

Treatment compliance will be reviewed by the investigator or designee at the TOC (Day 11) visit. Subjects (or subjects' legal representatives, if applicable) 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 21.3.8.3.

21.3.10.12 Assessment of Efficacy

Efficacy outcomes (Section 21.3.14.5.1) will be assessed by the investigator at the TOC (Day 11) and FU (Day 25) visits and any time there is suspicion of persistence or worsening of symptoms. Efficacy will be evaluated based on the following procedures:

- Vulvovaginal examination and rating of VVC signs on the VSS Scale by the investigator (see Section 21.3.10.7)
- Rating of vulvovaginal symptoms on the VSS Scale by the subject (see Section 21.3.10.8)

- Collection of vaginal samples for the following tests (see Section 21.3.10.6):
  - pH measurement (local)
  - 10% KOH testing for identification of yeasts (local)
  - Fungal culture for identification of species and susceptibility testing (central)
  - Additional tests for identification of other potential pathogens (local or central, depending on pathogen)
- Recording of any additional antifungal medication used by the subject (see Section 21.3.10.15)

All of the procedures above should be completed prior to administration of any new antifungal medication. **If there is suspicion of persistence or worsening of symptoms, subjects will be strongly discouraged from self-administering any treatment and will be instructed to visit the study center for a proper evaluation before initiating any new VVC treatment.** Ideally, if the severity of the symptoms allows based on the investigator's judgment, the initiation of antifungal therapy should be delayed until results from the vaginal culture are available to confirm that the episode is due to *Candida* spp. and not to other cause of vaginitis.

21.3.10.13 Sample Collection for Safety Laboratory Tests

Safety laboratory tests will be performed by a qualified central laboratory. Blood samples for safety laboratory tests will be collected at the TOC (Day 11) visit 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
- Blood urea Nitrogen (BUN)
- Total creatine phosphokinase (CPK)
- Aspartate aminotransferase (AST/SGOT)
- Alanine aminotransferase (ALT/SGPT)
- Gamma glutamyl transferase (GGT)
- Bilirubin (total, direct and indirect)
- Total protein

21.3.10.14 Vital Signs

Vital signs, including blood pressure (systolic and diastolic), heart rate, respiratory rate and body temperature will be measured at the Baseline (Day 1) and TOC (Day 11) visits as well as at unscheduled study visits, if needed.

21.3.10.15 Prior and Concomitant Medication Review

All medications (including prescription and over-the-counter medications, supplements, and herbal products) taken from Baseline (Day 1) through the TOC visit (Day 11) will be recorded on the subject's diary and eCRF. Only the use of other antifungal medications, medications used to treat vaginal bacterial or parasitic infections, topical vaginal medications or any other medications to treat a study drug-related AE will be recorded after the TOC visit through the last study visit (FU [Day 25]). 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 21.1 (Appendix A) of the Main Study for prohibited medications, medications to be administered with caution and further details for non-study treatments.

21.3.10.16 Adverse Event Monitoring

AEs will be recorded and reviewed at all scheduled and unscheduled study visits from the time the Informed Consent Form is signed in the Main Study through Follow up (Day 25). Subjects will record any AE on their study diary from Baseline (Day 1) through the TOC visit (Day 11).

21.3.11 Study Schedule

Detailed schedules of all study visits and procedures are presented in the Schedule of Visits and Procedures (**Sub-Study Table 1**).

Sub-Study Table 1: Schedule of Visits and Procedures (Study SCY-078-304S)

Visit	Baseline (Treatment)	Test of Cure	Follow-up	Unscheduled Visits[a]
Day (allowable window) **Study Procedures**	**Day 1**	**Day 11 (±3)**	**Day 25 (± 4)**	
Informed Consent[b]				
Assignment of Subject Number	X			
Inclusion/Exclusion criteria	X			
Abbreviated physical exam	X[c]	X		If needed
Urine pregnancy test[d]	X[c]			If needed
Vulvovaginal sample for KOH[e]	X	If needed	If needed	If needed
Vulvovaginal sample for fungal culture[e]	X[c]	If needed	If needed	If needed
Vulvovaginal sample for pH[e]	X[c]	If needed	If needed	If needed
Vulvovaginal sample for other pathogens[e]	X			If needed
Vulvovaginal exam[f] and rating of signs by the investigator	X[c]	X	If symptoms[g]	If needed
Rating of vulvovaginal symptoms by the subject	X[c]----------X		X	If needed
Study drug dosing and dispensing	X[h]			
Subject diary dispensing[i]	X			
Subject diary completion	X ----------X			
Study drug collection and review		X		
Subject diary collection and review		X		
Assessment of efficacy		X	X	
Sample collection for safety labs (hematology and blood chemistry)		X[j]		If needed
Vital Signs	X[c]	X		If needed
Prior & concomitant medication review	X[c]	X	X	X
Adverse event monitoring[k]	X[c]	X	X	X

Abbreviations: KOH = potassium hydroxide; VSS = vulvovaginal signs and symptoms

a. Unscheduled visits should be conducted anytime that there is indication of persistence or worsening of symptoms or an adverse event. If there is suspicion of persistence or worsening of symptoms, subjects will be strongly discouraged from self-administering any treatment and will be instructed to visit the study center for a proper evaluation before initiating any new VVC treatment.
b. Informed consent will be obtained for both the Main Study and this Sub-Study at the Screening visit of the Main Study.
c. These procedures are conducted as part of the Baseline (Day 1) visit for the Main Study and do not need to be repeated for the purpose of this study.
d. Results should be reviewed prior to the administration of the first dose of study drug.
e. Vulvovaginal specimens will be obtained at the Baseline (Day 1) visit for all subjects and at the TOC (Day 11) and FU (Day 25) visits if vulvovaginal symptoms have not improved or have worsened. Samples will be collected for pH determination and KOH testing as well as to rule out bacterial vaginosis and *Trichomonas vaginalis* (wet-mount or other, process locally at the site or at a local qualified lab). Testing for *Neisseria Gonorrhoeae, Chlamydia trachomatis* or *Herpes* virus may also be conducted if these pathogens are suspected (central laboratory). Samples for fungal culture should also be collected for processing at a central laboratory. Susceptibility testing will be done centrally for all positive cultures during the study. Samples should also be obtained any time that a subject experiences persistence or worsening of symptoms (i.e., unscheduled visits if needed).
f. If a subject is actively menstruating at a study visit that requires a vaginal exam, the visit should be rescheduled as soon as the subject's period ends but in no case more than 7 days after the initially

Visit	Baseline (Treatment)	Test of Cure	Follow-up	Unscheduled Visits[a]
Day (allowable window)	**Day 1**	**Day 11 (±3)**	**Day 25 (± 4)**	
Study Procedures				

scheduled visit.

g. 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.
h. Subjects will receive their first dose of study drug at the site at the Baseline (Day 1) visit and will be given study drug to self-administer their second dose at home. The two doses should be administered approximately 12 (±4) hours apart, preferably with or immediately after a meal.
i. Subject diaries will be used to rate vulvovaginal symptoms of infection on the VSS Scale and record second dose of study drug details, adverse events and concomitant medication use.
j. Conducted by the central lab.
k. Recorded from the time the Informed Consent Form is signed in the Main Study.

21.3.12 Safety Assessments and Monitoring

21.3.12.1 Definitions, Grading, Causality and Other General Details for Adverse Events

All specifications for AE definitions, grading, causality, reporting and other general details for safety assessment and monitoring that are provided in Section 16.0 of the Main Study protocol are applicable to this Nested Sub-Study except if in conflict with any of the sections provided below.

21.3.12.2 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 or accompanied by total bilirubin > 2 x ULN

21.3.12.3 Adverse Event Collection Timeframe

AEs and serious AEs (SAEs) will be recorded from Baseline (Day 1) through the Follow up (Day 25) visit. Subjects will record any AE on their study diary from Baseline (Day 1) through the TOC visit (Day 11).

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 investigator 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.

21.3.12.4 Procedures for Emergency Unblinding

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

21.3.13 Data Collection, Study Monitoring and Record Management

See Section 17.0 of the Main Study protocol for data collection, study monitoring and record management details.

21.3.14 Analytical Plan

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

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.

A Statistical Analysis Plan (SAP) describing all statistical analyses in detail will be provided as a separate document. The SAP will be finalized before full review of the data from this sub-study to avoid bias.

21.3.14.1 Sample Size Determination

The primary endpoint of the study is the percentage of subjects with Clinical Success (at least 50% reduction from Baseline in the total composite VSS score with no additional antifungal therapy required based on investigator's judgment) at the TOC visit. As this is a single arm sub-study, a statement regarding the Clinical Success rate and 95% confidence interval will be produced. It is estimated that 60 subjects will be included based upon published fluconazole failure rates. With a study of this size, if the Clinical Success rate for ibrexafungerp were 50%, this would correspond to a 95% confidence interval spanning from 36.8% to 63.2%. Given it is expected that the Clinical Success for ibrexafungerp in subjects who have already failed fluconazole will be low as these subjects had already failed to respond, a sub-study of this size is appropriate to assess the efficacy of ibrexafungerp in this patient population.

21.3.14.2 Analysis Populations

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

- **Intent-to-Treat (ITT) Population**: All ibrexafungerp-treated subjects.
- **Modified Intent-to-Treat (mITT) Population:** All treated subjects who have a positive culture for *Candida* species at Baseline.
- **Safety Population:** All randomized subjects who received at least one dose of study drug and who have at least one post-Baseline evaluation.

21.3.14.3 Handling of Missing Data and Early Withdrawals

For the efficacy analyses, subjects who do not have a TOC (Day 11) assessment will be assigned as treatment failures. For subjects who withdraw from the study early, every effort will be made to collect TOC (Day 11) visit information at the point of withdrawal.

21.3.14.4 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 EOFU visit date with missing stop dates or stop dates after the first dose of study drug will be considered concomitant medications.

21.3.14.5 Efficacy

21.3.14.5.1 Efficacy Assessments

The primary efficacy endpoint of the study is the percentage of subjects with Clinical Success (at least 50% reduction from Baseline in the total composite VSS score with no additional antifungal therapy required based on investigator's judgment) at the Test-of-Cure (TOC) visit.

Secondary efficacy endpoints include the percentage of subjects with Clinical Improvement at the TOC visit, the percentage of subjects with Clinical Cure at the TOC visit, the percentage of subjects with Mycological Eradication at the TOC visit, the percentage of subjects with both Clinical Cure and Mycological Eradication at the TOC visit, the percentage of subjects with Continued Clinical Success at the FU visit, and the absolute change in total composite VSS score from Baseline to the TOC and FU visits.

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

Clinical Outcomes

- Clinical Success: at least 50% reduction from Baseline in the total composite VSS score with no additional antifungal therapy required based on investigator's judgment
- Clinical Improvement: partial or complete resolution of signs and symptoms (total composite score ≤ 1 on the VSS Scale) with no additional antifungal therapy required based on investigator's judgment
- Clinical Cure: complete resolution of signs and symptoms (total composite score of 0 on the VSS Scale) with no additional antifungal therapy required based on investigator's judgment
- Continued Clinical Success: sustained resolution of signs and symptoms in subjects who achieved Clinical Success at the TOC visit
- Clinical Failure: persistence and/or worsening of signs and symptoms or need for additional antifungal therapy

Mycological Outcomes

- Mycological Eradication: negative culture for growth of *Candida* species.
- Mycological Persistence: positive culture for growth of *Candida* species.

21.3.14.5.2 Efficacy Analyses

The primary endpoint, the percentage of subjects with Clinical Success at TOC, will be assessed on the mITT population and will present the Clinical Success rate and the 95% confidence interval calculated using the method of Clopper and Pearson.[1] Missing data for the primary endpoint will be imputed as failure. In addition, the Clinical Success rate

and 95% confidence interval will be calculated where subjects with missing values will be removed from the analysis.

All other efficacy data will be summarized, but not subject to formal statistical analysis.

21.3.14.6 Safety

21.3.14.6.1 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 in the Main Study. An abbreviated physical examination, including general appearance and an overall examination of body systems, will be conducted at Baseline (Day 1), at the TOC (Day 11) visit, and at unscheduled visits, if needed. Vital signs, including blood pressure (systolic and diastolic), heart rate, respiratory rate and body temperature will be measured at the Baseline (Day 1) and TOC (Day 11) visits, and at unscheduled visits, if needed. Safety laboratory tests (hematology and blood chemistry) will be measured at the TOC (Day 11) visit and at unscheduled visits, if needed. All prior and concomitant medications taken before Baseline (Day 1) through the TOC (Day 11) visit will be recorded. Only the use of other antifungal medications, medications used to treat vaginal bacterial or parasitic infections, topical vaginal medications, or any other medications to treat a study drug related AE will be recorded after the TOC (Day 11) visit through the last study visit (FU [Day 25]).

Safety procedures are described in Section 21.3.10 and safety assessments are described in Section 21.3.12.

21.3.14.6.2 Safety Analyses

No formal statistical analysis is planned for the safety data. Safety presentations 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.

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 for laboratory tests.

21.3.15 Ethics and Protection of Human Patients

All ethical and other protocol-specified details for the protection of human subjects discussed in the Main Study (Section 19.0) are applicable to this Nested Sub-Study.

21.3.16 References

1. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934 Dec;26(4):404-413.