SCYNEXIS, Inc.

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

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Statistical Analysis Plan

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Prepared by:

PPD
Unit 1101, Henderson Metropolitan,
No. 155 Tianjin Road, Huangpu District,
Shanghai 200001, China

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List of Abbreviations

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	Analysis of variance
AST	aspartate aminotransferase
BL	baseline
BMI	body mass index
CI	confidence interval
CLSI	Clinical and Laboratory Standards Institute
CMH	Cochran Mantel Haenszel
CRF	case report form
eCRF	electronic case report form
EOFU	end of follow-up
EQ-5D	Euro Quol 5 Dimensions
EQ-5D-5L	Euro Quol 5 Dimensions 5-Level Version
FLU	fluconazole
FSDS	Female Sexual Distress Scale
FUP	follow-up
ICF	Informed Consent Form
ID	identification
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	Interactive web-based response system
KOH	potassium hydroxide
LOCF	last observation carried forward
LS	least squares
MCS	Mental Component Summary Score
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
MIC50	minimum inhibitory concentration required to inhibit the growth of 50% of organisms
MIC90	minimum inhibitory concentration required to inhibit the growth of 90% of organisms
mITT	modified intent to treat
MMRM	Mixed-Effect Model for Repeated Measure
NRI	non-responder imputation
PAE	prior adverse event
PCS	Physical Component Summary Score
PI	principal investigator
PP	per protocol
PR	potential recurrence
PT	preferred term
QD	once a day
QOL	Quality of Life
RVVC	recurrent vulvovaginal candidiasis

SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SE	Standard error
SF-36	Short Form Health Survey
SOC	system organ class
SS	safety set
TEAE	Treatment emergent adverse event
TOC	test of cure
UK	unknown
ULN	upper limit of normal
UNK	unknown
VAS	Visual analogue scale
VSS Scale	vulvovaginal signs and symptoms scale
VVC	vulvovaginal candidiasis
WHO-DD	World Health Organization Drug Dictionary Enhanced

1. Introduction

Vulvovaginal candidiasis (VVC) is a common fungal infection caused by *Candida spp.* and is a significant morbidity condition in women from all social classes. VVC can be an acute, chronic, recurrent, or persistent condition that can involve the vulva, vagina, and adjacent crural areas. It affects about 70%-75% of women on at least one occasion over a lifetime. Approximately 40%–50% of women will experience a recurrence and 5% to 8% of adult women have a recurrent vulvovaginal candidiasis (RVVC).

Current treatments for VVC include topical antifungals and the use of prescription oral antifungals such a single dose 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.

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. 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. 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.

Ibrexafungerp (formerly known as SCY-078) is a member of a new class of antifungal agents and is an orally active, semi-synthetic, triterpenoid derivative of the natural product enfumafungin. Time-kill studies have demonstrated that ibrexafungerp (SCY-078) has in vitro fungicidal activity against *Candida spp*. isolates similar to that observed with the echinocandins. In addition, the safety and efficacy of ibrexafungerp (SCY-078) have been proved through many non-clinical programs and phase I/II studies.

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.

2. Objectives

2.1. Primary Objectives

- 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.

2.2. 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 Test of Cure (TOC).

2.3. 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.

3. Investigational Plan

3.1. Overall Study Design and Plan

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.

The schedule of study assessments is presented in Appendix 1.

3.2. Study Endpoints

3.2.1. Primary Endpoints

- 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 Week 24 (TOC).

3.2.2. 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 Vulvovaginal Signs and Symptoms [VSS] Scale and a culture positive for Candida spp. that required antifungal treatment) up to Week 24 (TOC).

3.2.3. Other Secondary Endpoints:

Efficacy as measured by:

- The percentage of subjects with no Mycologically Proven Recurrence up to 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 up to Week 4, Week 8, Week 12 and Week 36 (EOFU);
- The percentage of subjects with no Mycologically Proven or Presumed Recurrences up to Week 4, Week 8, Week 12, Week 24 (TOC) and Week 36 (EOFU);
- The proportion of subjects in four ordered categories related to the number of Recurrences (Mycologically Proven, Presumed or Suspected) of VVC from Baseline (Day 1) to Week 24 (TOC) and Week 36 (EOFU). The three categories of recurrence are defined as (i) 0 episode, (ii) 1 episode, (iii) 2 to 3 episodes, and (iv) ≥ 4 episodes;
- The absolute number of Mycologically Proven, Presumed or Suspected Recurrences from Baseline (Day 1) to Week 24 (TOC) 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.

3.3. Treatments

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 *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 entered into the Prevention of Recurrence Phase and 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. Subjects will record study drug dosing details in their study diary.

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. 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) at Baseline (Day 1). A detailed analysis plan for the Nested Sub-study will be provided in the Appendix 4.

4. General Statistical Considerations

Continuous data will be described using descriptive statistics (i.e. n, mean, standard deviation (SD), median, minimum, and maximum). Categorical data will be described using the subject count and percentage in each category. For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean and median will be displayed to one level of precision greater than the data collected. Standard deviation / standard error will be displayed to two levels of precision greater than the data collected. P-values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as "<0.001." If a p-value is greater than 0.999 it will be reported as ">0.999." Data will be displayed in all listings sorted by treatment group.

Subjects will be identified in the listings by the subject identification number concatenated with the investigator number.

When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted "Missing" will be included in count tabulations where specified on the shells to account for dropouts and missing values. The denominator for all percentages will be the number of subjects in that treatment within the analysis set of interest, unless otherwise specified.

Unless otherwise specified, baseline will be defined as the last non-missing assessment prior to or on the date (and time if appropriate) of the first dose of study drug. Change from baseline is defined as post-baseline value – baseline value.

The study day will be calculated as follows:

If the assessment date occurs on or after the date of the first dose of study drug:

Study day = assessment date – first dose date + 1.

If the date of interest occurs before the date of the first dose of study drug:

Study day = assessment date – first dose date

There is no study day 0.

All analyses will be conducted using SAS Version 9.3 or higher. All statistical tests will be two-sided and interpreted at a 5% significance level.

This statistical analysis plan is created for the main study. Regarding the detailed description of the statistical analysis of the nested sub-study, please refer to the Appendix 4.

4.1. Sample Size

The primary endpoint of the study is the percentage of subjects with documented Clinical Success up to Week 24 (TOC). 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. Enrolment into the Acute Phase will be discontinued when approximately 240 subjects have been randomized.

4.2. Randomization, Stratification and Blinding

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.

An interactive web-based response system (IWRS) will be used to administer the randomization schedule. Biostatistics will generate the randomization schedule using SAS® software Version 9.3 or later (SAS Institute Inc, Cary, North Carolina) for IWRS, which will link sequential subject randomization numbers to treatment codes.

Neither the subjects nor the investigators will be aware of the treatment assignment for the subjects. The study drugs will be identical in number and appearance. Blinding will be maintained throughout the study by use of active or placebo dosage forms of similar appearance.

A subject's treatment assignment will not be broken until the end of the study unless medical treatment of the subject depends on knowing the study treatment the subject received. In the event that the blind needs to be broken because of a medical emergency, the investigator may unblind an individual subject's treatment allocation. As soon as possible, the investigator should first contact the medical monitor to discuss the medical emergency and the reason for revealing the actual treatment received by that subject. No investigator is in full rights to unblind a subject on medical reasons without prior consultation with the sponsor or medical monitor.

Eligible 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).

4.3. Analysis Set

Intent-to-Treat (ITT) Set: All randomized subjects who received at least one dose of study drug (ibrexafungerp or placebo).

Modified Intent-to-Treat (mITT) Set: All randomized subjects who received at least one dose of study drug (ibrexafungerp or placebo), who have a confirmed mycological culture for yeast at Screening and a negative culture for yeast at Baseline (Day 1).

Per-Protocol (PP) Set: All mITT 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 Set (SS): All randomized subjects who received at least one dose of study drug (ibrexafungerp or placebo) and who have at least one post-baseline evaluation.

4.4. Handing of missing data

4.4.1. Non-Responder Imputation (NRI) for Categorical Responses

For clinical responses which described in section 8.1, and 8.2.1, a subject who has not previously experienced a failure response of the endpoint of interest and does not have the required assessment of potential recurrence data at Week 4 (or Week 8, Week 12, Week 24 (TOC) and Week 36 (EOFU)) for any reason will be considered as failure in the analysis of the specified time point. If one or more of the required assessments of potential recurrence are not completed within Week 4 (or Week 8, Week 12, Week 24 (TOC) and Week 36 (EOFU)), the subject will be considered as failure. Randomized and took at least 1 study treatment patients without at least 1 post-baseline observation will also be defined as failure for the NRI analysis.

For mycological outcome, subjects will be considered a non-responder for the NRI analysis if their mycological outcome cannot be determined due to early termination before the specified visit or missing mycological data at the specific visit. Randomized subjects without at least 1 post-baseline observation will also be defined as non-responder for the NRI analysis.

Randomized subjects without study treatment will be excluded from all analysis.

The NRI may be applied at any time point specified for analysis.

4.4.2. Last Observation Carried Forward (LOCF)

A LOCF analysis will be performed on health outcome variables, including EQ-5D Summary Index and EQ VAS, all 8 scale scores and 2 overall scores of SF-36, and FSDS total score. The last non-missing post-baseline observation will be carried forward to the corresponding endpoint for evaluation. For patients that take rescue therapy, their last non-missing observation up to the date of the rescue medication will be carried forward to the corresponding endpoint for evaluation. Randomized patients without at least 1 postbaseline observation will not be included for evaluation.

5. Subject Disposition

5.1. Disposition

A flowchart diagram includes the number of subjects who screened, subjects who screen failed before acute phase, subjects who entered acute phase, subjects who discontinued after acute phase,

subjects who entered the nested sub-study, subjects who entered the prevention of recurrence phase, will be presented.

For subjects who entered the nested sub-study, the following categories should be presented: subjects in each analysis set (ITT, mITT, SS), subjects who completed TOC visit, subjects who completed the study, subjects who discontinued from the study, and the reasons for study discontinuation.

For subjects who entered the prevention of recurrence phase, the following categories should be presented: subjects in each analysis set (ITT, mITT, PP, SS), subjects who completed TOC visit, subjects who completed the study, subjects who discontinued from the study, and the reasons for study discontinuation.

A disposition table of subjects includes the number and percentage of subjects for the following categories: subjects in each analysis set (ITT, mITT, PP, SS), subjects who completed TOC visit, subjects who completed the study, subjects who discontinued from the study, and the reasons for study discontinuation will be presented by the ITT and mITT sets. All percentages will be based on the number of subjects in each corresponding set.

The reason for study discontinuation may include any of the following: Absence of culture-confirmed Candida spp. infection from the sample reviewed at Baseline, Adverse Event, Lost to Follow-up, Physician Decision, Pregnancy, Study Terminated by Sponsor, Withdrawal by Parent or Guardian, Withdrawal by Subject, Other, Death, Trial Screen Failure.

Subject disposition data will be presented in a listing.

5.2. Protocol Deviations

The investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate IRB, except when necessary to eliminate immediate hazards to the subject or when the change(s) involve(s) only logistical or administrative aspects of the study.

Significant protocol deviations will be defined in the significant protocol deviations rules document. Each significant deviation will be assigned a rule number. As the study is ongoing, additional significant protocol deviations can also be spontaneously identified or defined by the sponsor and/or the project team during the regularly planned study deviation review meetings and the significant protocol deviations rules document can be updated.

All protocol deviations will be reviewed and assessed as to significance and severity for the purposes of analysis prior to the database lock.

All major protocol deviations (i.e. resulting in exclusion of the subjects from one or more analysis) will be summarized using the ITT and mITT sets.

Major protocol deviations will also be presented in a listing.

6. Demographics and Baseline Characteristics

6.1. Demographics

A summary of the following demographics will be presented for the subjects in ITT set and mITT set, respectively.

- Age (years);
- Age group (<18 years, 18 -<36 years, 36 -<50 years, 50 -<65 years, ≥65 years);
- Sex (Female);
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and Other);
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino);
- Country [USA (United States), BGR (Bulgaria), RUS (Russia), POL (Poland)];
- Geographical location (USA, EX-USA);
- BMI (kg/m²);
- BMI group (Underweight <18.5 kg/m², Normal 18.5-<25 kg/m², Overweight 25-<30 kg/m², Obese 30-<40 kg/m² and Morbidly Obese ≥40 kg/m²);
- BMI group (≤35 kg/m² and >35 kg/m²).

The age collected in CRF will be used for analysis if it is non-missing. If the age is not collected in the CRF, the age in years is calculated using the date of the informed consent and date of birth.

$$\text{Age (years)} = [(\text{Informed Consent Date} - \text{Date of Birth} + 1) / 365.25].$$

BMI is calculated as

$$\text{BMI} = (\text{body weight in kilograms}) / (\text{height in meters})^2.$$

Demographics for all subjects in the ITT set will be presented in a listing.

6.2. Baseline Characteristics

A summary of the following baseline characteristics will be presented for subjects in the ITT and mITT sets, respectively.

- Number of recurrent VVC episodes in the prior year;
- Uncontrolled diabetes mellitus (Yes or No);
- Candida species at screening (by Genus species);
- Candida species at baseline (by Genus species);
- Composite score of the vulvovaginal signs and symptoms at screening;

- Severity of VVC at screening (the composite score of the vulvovaginal signs and symptoms at screening '4 - 7', '8 - 12', and '>=13');
- Severity of VVC at screening (the composite score of the vulvovaginal signs and symptoms at screening <7, >=7);
- Total score of Female Sexual Distress Scale at baseline;
- Categorical responses of the 5 EQ-5D dimensions, EQ VAS score, and EQ-5D index score at baseline;
- SF-36 PCS and MCS;
- Fertility Status (Surgically Sterile/Infertile, Post-Menopausal, Potentially Able to Bear Children);
- Method of Birth Control (Barrier Methods Only, Oral Contraceptives, Depo Contraceptives (Implants/Injectables), IUD, Abstinence, Vaginal Ring, Vasectomized Partner, None, Other);

A separate summary table will be presented to include MIC range, mode, MIC50, and MIC90 by treatment group and geographical region (USA or Ex-USA) for the following MIC results from 2 different methods, CLSI and EUCAST, respectively:

- MIC results for SCY-078 and fluconazole (FLU) at 24 hours against candida species isolates obtained at Screening for all subjects in the ITT, mITT and PP sets;
- MIC results for SCY-078 and fluconazole (FLU) at 48 hours against candida species isolates obtained at Screening for all subjects in the ITT, mITT and PP sets.
- MIC results for SCY-078 and fluconazole (FLU) at 24 hours against candida species isolates obtained at Baseline for all subjects in the ITT set;
- MIC results for SCY-078 and fluconazole (FLU) at 48 hours against candida species isolates obtained at Baseline for all subjects in the ITT set.

Baseline characteristics for all subjects in ITT set will be presented in a listing.

6.3. Medical History

Medical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA; Version 19.1 or higher). A frequency summary (number and percentage) of subjects with at least one medical history will be presented by system organ class (SOC), and preferred term (PT), with SOCs sorted in alphabetical order and PTs within each SOC in descending order of frequency for all subjects in the ITT and mITT sets.

In addition, A summary of other vulvovaginal conditions (Selected SOC and PTs) will be presented by SOC, and PT for subjects in the mITT set.

A by-subject listing of medical history will be provided for all subjects in the ITT set.

6.4. Inclusion and Exclusion Criteria

Prior to both screening and randomization, the investigator will assess if the subject fulfills all of the inclusion and none of the exclusion criteria outlined in the protocol (sections 11.1 and 11.2). The specific inclusion criterion not met or exclusion criterion which was met will be recorded in the eCRF.

7. Treatments and Medications

7.1. Prior and Concomitant Medications

All prior and concomitant medications taken from 28 days before screening through the Week 24 (TOC) visit will be recorded. 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)).

A summary with the number and percentage of subjects who took medications will be presented by WHO therapeutic drug class and generic drug name for those subjects who discontinued before entering the prevention of recurrence phase or the nested sub-study. In addition, a by-subject listing of medications will be provided.

For the purpose of inclusion in prior and/or concomitant medication tables, incomplete medication start and stop dates will be imputed as follows:

Missing start dates (where UK, UKN and UNKN indicate unknown or missing day, month and year respectively):

- UK-MMM-YYYY: Assume 01-MMM-YYYY. If the month and year are the same as the first dose of study drug month and year, then assume the date of first dose of study drug;
- UK-UKN-YYYY: If the year is prior to the year of first dose of study drug, assume 01-JAN-YYYY of the collected year. If the year is the same as the first dose of study drug year, then assume the date of first dose of study drug;
- UK-UKN- UNKN: Assume date of first dose of study drug.

Missing stop dates for concomitant medications data will be handled as follows (where UK, UKN and UNKN indicate unknown or missing day, month and year respectively):

- UK-MMM-YYYY: Assume the last day of the month;
- UK-UKN-YYYY: Assume 31-DEC-YYYY;
- UK-UKN- UNKN: Assume ongoing and leave it missing.

All prior and concomitant medications will be coded using the current version of the World Health Organization Drug Dictionary Enhanced (WHO-DD) and summarized by treatment group based on the ITT and mITT sets.

7.1.1. Prior Medications

Prior medications are defined as medications taken and stopped prior to the first dose of study drug. The number and percentage of subjects who took prior medications will be presented by WHO therapeutic drug class and generic drug name.

In addition, a summary of the following will be presented for subjects in the ITT set:

- Antibiotic use 30 days before baseline visit;
- Systemic steroid use 30 days before baseline visit;
- Antifungal medications use 1 year prior to baseline visit.

7.1.2. Concomitant Medications

Concomitant medications are defined as medications started on or before the EOFU visit date with missing stop dates or stop dates after the first dose of study drug.

A summary showing the number and percentage of subjects who took concomitant medications will be presented by WHO therapeutic drug class and generic drug name.

A by-subject listing of prior and concomitant medications will be provided.

7.1.3. Rescue Antifungal Medications

The number and percentage of subjects who took rescue antifungal medication, prior or on TOC visit, after TOC visit but before or on EOFU visit, will be presented for the ITT and mITT sets.

A by-subject listing of rescue antifungal medications will be provided.

7.2. Study Treatments

Please refer to Section 3.3 for the details of the study treatment.

Data related to the study treatment will be presented in a listing.

7.2.1. Acute Phase

7.2.1.1. Exposure of Fluconazole

The duration of treatment of fluconazole (days) is calculated as (last dose date of fluconazole – first dose date of fluconazole + 1).

The actual fluconazole dose taken across the acute phase will be calculated as the number of fluconazole dispensed minus the number of fluconazole returned. If the fluconazole bottle was not returned, the dose diary data will be considered for the actual fluconazole dose calculation. When subject answered no dose missing, we can assume the actual fluconazole dose is 3 tablets. When subject answered only 1 dose missing, we can assume the actual fluconazole dose is 2 tablets. When subject answered 2 doses missing, we can assume the actual fluconazole dose is 1 tablet. When subject answered 3 doses missing, we can assume the actual fluconazole dose is 0 tablet.

The actual fluconazole dose is missing when subject didn't answer at least one missing dose question.

The duration of treatment of fluconazole, and the actual fluconazole doses will be summarized descriptively for all screened subjects.

All this exposure information of fluconazole will be presented in a listing.

7.2.1.2. Treatment Compliance of Fluconazole

Treatment compliance of fluconazole is defined as the ratio of the actual fluconazole dose to the planned dose, in terms of percentage. Treatment compliance of fluconazole will be summarized descriptively based on all screened subjects.

Treatment compliance = the actual fluconazole dose / the planned dose (3 tablets) *100%.

The treatment compliance will be classified as 0%, 33.3%, 66.7%, and 100%. This categorical data will be summarized with the frequency and percentage of subjects based on all screened subjects.

Non-compliance with dose regimen (example 2 tablets taken as a single dose) will be captured based on investigator's review of subject diary.

7.2.2. Prevention of Recurrence Phase

7.2.2.1. Study Participation Calculation and Extent of Exposure

The duration of study treatment (days) is calculated as (treatment end date – treatment start date + 1). The treatment start date is the date of first dose of study treatment. For patients who have completed or discontinued study treatment, the treatment end date is the date of last dose of study treatment recorded on end of Study page.

The duration of study participation (days) is calculated as date of Study Completion/Termination recorded on the End of Study page – Inform consent date + 1. If the date of Study Completion/Termination on the End of Study page is missing, or if a subject is lost to follow-up, the latest available visit date will be used.

The cumulative study drug doses taken across the Prevention of Recurrence phase is defined as the total number of study drug dispensed minus the total number of study drug returned. If any of study drug bottle not returned, the missing doses as recorded in the Dosing page of eCRF will be considered for the cumulative study drug doses calculation. For the specified drug dispensation period, the cumulative study doses for that period can be calculated as (6 – the number of times subjects answered dose missing) × 2 tablets each time. For example, when subject answered only 1 dose missing, we can assume the cumulative study drug dose for the specified period is 5 times × 2 tablets each time = 10 tablets. The cumulative study drug dose will set to be missing when subject didn't answer at least one missing dose question.

The duration of study treatment, the duration of study participation, the cumulative study drug doses by treatment will be summarized descriptively.

All this exposure information will be presented in a listing.

7.2.2.2. Treatment Compliance

Treatment compliance of study drug is defined as the ratio of the actual study dose to the planned dose, in terms of percentage. Treatment compliance will be summarized descriptively.

Treatment compliance = the cumulative study drug dose / the planned dose (24 tablets) *100%.

The treatment compliance will be classified as <80% and 80% to 100%. This categorical data will be summarized with the frequency and percentage of subjects by treatment group.

Non-compliance with dose regimen (example only 1 tablet taken as a single dose) will be captured based on investigator's review of subject diary.

8. Efficacy Analysis

The primary efficacy and secondary efficacy endpoints will be performed on the ITT, mITT and PP sets. The ITT analyses will be considered primary; the mITT and PP analyses will be considered supportive of the primary analyses on the ITT population. The denominator for all percentages will be the number of subjects in that treatment within the analysis set of interest, unless otherwise specified.

8.1. Primary Endpoint

The primary efficacy endpoint is defined as the proportion of ITT subjects who have documented Clinical Success (defined as subjects having a TOC evaluation and no Mycologically Proven, Presumed or Suspected Recurrences of VVC) up to Week 24 (TOC).

Clinical success will be assessed according to the following definitions:

- Clinical success: Subjects having a TOC evaluation and no Mycologically Proven, Presumed or Suspected Recurrences of VVC prior to or at the TOC visit.
- Clinical failure: Mycologically Proven, Presumed or Suspected Recurrences of VVC prior to or at the TOC visit. For the subject who early terminated before TOC visit, the subject is considered a clinical failure.

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. It also includes an episode of VVC that requires antifungal treatment and have a total VSS composite score lower than 3 regardless of mycological results.

8.1.1. Primary Analysis

The primary efficacy analysis will be performed on the ITT set at the TOC visit and will compare the proportion of subjects, in the treatment and placebo groups, who have documented Clinical Success up to Week 24 (TOC).

The number and percentage of subjects with documented clinical success up to the TOC visit will be presented by treatment group. Meanwhile, the number and percentage of subjects with clinical

failure will be presented by the recurrence categories. A Cochran Mantel Haenszel (CMH) test adjusted for Country and uncontrolled diabetes mellitus (Yes or No) at baseline will be performed to assess the statistical significance of a difference between treatment groups in the primary efficacy analysis. Mathematically stated:

H_0: Clinical Success Rate up to Week 24 (TOC) $_{\text{Oral ibrexafungerp 300-mg dose}}$ = Clinical Success Rate up to Week 24 (TOC) $_{\text{Placebo}}$

H_1: Clinical Success Rate up to Week 24 (TOC) $_{\text{Oral ibrexafungerp 300-mg dose}}$ ≠ Clinical Success Rate up to Week 24 (TOC) $_{\text{Placebo}}$

The p-value, relative risk and 95% confidence interval (CI) will be presented in the ibrexafungerp 300-mg treatment arm compared to the placebo arm. Subjects who have one or more of the required assessments of potential recurrence not completed prior to or at Week 24 (TOC) visit or subjects who withdraw from the study early will be imputed using the imputation rules described in Section 4.4.1.

A sensitivity analysis using the ITT set will be performed where subjects with the imputed clinical outcome will be removed from the analysis.

Subgroup analyses will be performed in the ITT set depending on BMI category (≤35 kg/m² or >35 kg/m²), geographic region (USA and EX-USA), Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and Other), Uncontrolled diabetes mellitus (Yes or No), Ethnicity (Hispanic or Latino, Not Hispanic or Latino), Number of recurrent VVC episodes in the prior year (<4 times, =>4 times) and Candida species at screening (by Genus species), severity of VVC at screening (2 categorizations of the composite score of the vulvovaginal signs and symptoms at screening will be used to evaluate the severity of VVC at screening: <7, >=7 and '4 - 7', '8 - 12', and '>=13').

The same inferential analysis employing the same methods as for the primary analysis will be performed for the mITT set and PP set to assess clinical success rate up to the Week 24 (TOC). Subjects whose results are missing at Week 24 (TOC) and subjects who withdraw from the study early will be imputed using the imputation rules described in Section 4.4.1. No adjustment of type I error will be performed as these analyses are considered supportive to the primary analysis.

8.2. Secondary Efficacy Endpoints

8.2.1. Clinical Response

The same inferential analysis employing the same methods as for the primary analysis will be performed for ITT, mITT, and PP sets to assess below endpoints.

- 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) up to Week 4, Week 8, Week 12, Week 24 (TOC), and Week 36 (end of follow-up [EOFU]);

- The percentage of subjects with no Mycologically Proven, Presumed or Suspected Recurrences up to Week 4, Week 8, Week 12 and Week 36 (EOFU);
- The percentage of subjects with no Mycologically Proven or Presumed Recurrences up to Week 4, Week 8, Week 12, Week 24 (TOC) and Week 36 (EOFU);

For each specified timepoint, any clinical assessment outcomes at or before the specified visit will be counted. The imputation rules described in Section 4.4.1 will be used for the NRI analyses.

Analysis of time to first recurrence (Mycologically Proven, Presumed or Suspected) and time to first Mycologically proven recurrence of VVC through EOFU will use Kaplan-Meier method to estimate the median recurrence time and its 2-sided 95% CIs based on the ITT, mITT, and PP sets. The time to first recurrence (Mycologically Proven, Presumed or Suspected) and time to first Mycologically proven recurrence of VVC is defined as time (days) from first dose of study drug to the first recurrence (Mycologically Proven, Presumed or Suspected) and first Mycologically proven recurrence of VVC, respectively. Subjects who completed the study will be censored at the last visit date if no previously recurrence of VVC experienced. Subjects who discontinued early will be censored at the last available assessment if no previously recurrence of VVC experienced. Subjects who missed any required assessment of potential recurrence will be censored at the last available assessment before the first missed assessment if no previously recurrence of VVC experienced. If there was no post-baseline assessment of potential recurrence, subjects will be censored at the first dose date of study treatment.

Kaplan-Meier curves for time to the first recurrence (Mycologically Proven, Presumed or Suspected) of VVC and time to first Mycologically proven recurrence will be provided by treatment group based on the ITT, mITT, and PP sets.

The summary of the absolute number of recurrences from Baseline (Day 1) to Week 24 (TOC) and Week 36 (EOFU) will be presented by recurrence categories and overall, a two-way analysis of variance (ANOVA) model including effects for treatment group and Country will be performed. For individual treatment group and ibrexafungerp 300-mg BID comparison versus placebo, the least squares mean, associate standard error (SE), 95% confidence interval and corresponding p-value will be presented. Additionally, same analysis will be performed to only include those subjects who completed the specified visit based on the ITT set.

For the below ordered categorical endpoint, a proportional odds model will be fitted accounting for the effects of treatment, Country, and uncontrolled diabetes mellitus (Yes or No) at baseline. 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. The p-value, relative risk and 95% CI will be presented in the ibrexafungerp 300-mg treatment group compared to the placebo arm.

- The proportion of subjects in four ordered categories related to the number of Recurrences (Mycologically Proven, Presumed or Suspected) of VVC from Baseline (Day 1) to Week 24 (TOC) and Week 36 (EOFU). The four categories of recurrence are defined as (i) 0 episode, (ii) 1 episode, (iii) 2 to 3 episodes, and (iv) ≥ 4 episodes

8.2.2. Mycological outcomes

The percentage of subjects with mycological eradication (negative culture for growth of Candida species) at Baseline, Week 12, Week 24 (TOC) and Week 36 (EOFU) visits will be analyzed based on ITT, mITT, and PP sets using the same inferential analysis employing the same methods as for the primary analysis as noted in Section 8.1.1. The subjects with missing specified visit data for the mycological outcome will be imputed as mycological persistence using the NRI method described in Section 4.4.1.

Mycological outcomes will be assessed at the specified visit according to the following definitions.

- Mycological Eradication: A subject with negative culture for Candida species;
- Mycological Persistence: A subject with a positive culture for Candida species.

In addition, a sensitivity analysis will be conducted based on the ITT set where subjects with the imputed mycological outcome using the NRI method at the specified visit will be removed from the analysis.

In addition, a summary table will be presented to include MIC range, mode, MIC50, and MIC90, based on the ITT, mITT, and PP sets by treatment group and geographical region (USA or Ex-USA) for the following MIC results from 2 different methods, CLSI and EUCAST, respectively:

- MIC results for SCY-078 and fluconazole (FLU) at 24 hours against candida species isolates obtained at Week 12, Week 24 (TOC) and Week 36 (EOFU);
- MIC results for SCY-078 and fluconazole (FLU) at 48 hours against candida species isolates obtained at Week 12, Week 24 (TOC) and Week 36 (EOFU) visits.

8.2.3. Quality of Life Analysis

Quality of life 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 5-Level Version (EQ-5D-5L), Short Form Health Survey (SF-36) and Female Sexual Distress-Revised Scale (FSDS).

8.2.3.1. Euro Quol 5 Dimensions 5-Level Version

The EQ-5D-5L essentially consists of 2 parts: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive system comprises five dimensions: mobility, selfcare, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, unable to/extreme problems. The EQ VAS records the patient's self-rated health on a scale from 0-100 where 100 is the 'best imaginable health state' and 0 is the 'worst imaginable health state'. Additionally, an EQ-5D summary index will be calculated to reflect how good or bad a health state, which is defined by

combining one level from each of the five dimensions, is according to the preferences of the general population of a country/region. The EQ-5D index value is derived by applying a formula that attaches values (weights) to each of the levels in each dimension. The index values will be selected from the value sets which can be obtained from EuroQol office, refer to Appendix 2 for the samples of the value sets for this study. The value sets contain the index values for all possible EQ-5D health states for each country/region. If a standard EQ-5D-5L value set is not available for a specified country/region, it should discuss with client to select an EQ-5D-5L value set for a country/region that most closely approximates the country/region investigated. No missing dimension will be imputed.

A summary of the number and percentage of subjects by categorical responses of the 5 EQ-5D dimensions will be presented by treatment and by visit.

EQ-5D Summary Index and EQ VAS will be summarized by treatment and by visit descriptively. Change from Baseline to Week 12, Week 24 (TOC) and Week 36 (EOFU) in EQ-5D Summary Index and EQ-5D VAS will be analyzed and reported using an Mixed-Effect Model for Repeated Measure (MMRM) analysis model, using the ITT, mITT, and PP sets (one such analysis for all post-baseline data, grouped by time point), will be used to compare the difference between treatment groups. The model will include treatment group, Country, visit, uncontrolled diabetes mellitus (Yes or No) and the treatment-by-visit interaction as classification variables and the baseline value as covariate. An unstructured covariance matrix will be used. Based on this modeling, a point estimate, associate SE, 95% CI, and corresponding p-value will be provided for least squares (LS) mean treatment difference versus placebo at all scheduled timepoints. Degrees of freedom will be calculated using the Kenward-Roger procedure.

In addition, an analysis of covariance (ANCOVA) model will be used having treatment group, Country and uncontrolled diabetes mellitus (Yes or No) as classification variables, and the baseline value as the continuous covariate as a sensitivity analysis, including and excluding the imputed values as the LOCF approach described in section 4.2, respectively, for change from baseline of EQ-5D Summary Index and EQ VAS and for each scheduled timepoints. For each treatment and treatment comparison versus placebo, the least squares mean, associate standard error (SE), 95% confidence interval and corresponding p-value will be presented.

8.2.3.2. Short Form Health Survey

A score will be calculated for each of the 8 scales in SF-36. Each scale score ranges from 0 to 100, with higher score reflecting less disability. The partially missing scores may be imputed as described in Appendix 3 and used in the summary and analysis. 2 overall scores will be further derived: Physical Component Summary score (PCS) and Mental Component Summary score (MCS). The summary scores range from 0 to 100, with higher scores indicating better levels of function and/or better health. See scoring algorithm in Appendix 3. All 8 scale scores and 2 overall scores will be summarized by visit. Change from Baseline in scale scores, PCS, and MCS will be analyzed and reported using the same MMRM and ANCOVA model as specified for the change in EQ-5D Summary Index in Section 8.2.3.1.

8.2.3.3. Female Sexual Distress Scale

The Female Sexual Distress Scale (FSDS) is a validated instrument that measures sexually related personal distress in women. The FSDS is a 13-item self-administered questionnaire that addresses different aspects of sexual distress. Every item requires an answer that is then rated as 0–4 (never [0], rarely [1], occasionally [2], frequently [3], or always [4]). The total score ranges from 0 to 52, and provides a measure of sexual distress, with a higher score corresponding to a higher level of sexual distress. No missing dimension will be imputed.

FSDS total score will be summarized by treatment and by visit descriptively. Change from Baseline in FSDS total score will be analyzed and reported using the same MMRM and ANCOVA model as specified for the change in EQ-5D Summary Index in Section 8.2.3.1.

In addition, FSDS total score will be classified as '<11' and '>=11'. This categorical data will be summarized with the frequency and percentage of subjects by treatment group at each scheduled visit. In addition, this categorical data will be summarized in shift tables comparing the results at post-treatment study scheduled visits with those at the baseline visit.

8.2.4. Composite Score of the Vulvovaginal Signs and Symptoms

The composite score of the vulvovaginal signs and symptoms and Change from Baseline values to Week4, Week 8, Week 12, Week 24 (TOC), and Week 36 (EOFU) will be summarized by treatment and by visit descriptively.

The composite score of the vulvovaginal signs and symptoms will be classified as '0', '1', '2', and '>=3'. This categorical data will be summarized with the frequency and percentage of subjects by treatment group at each scheduled visit. When there are multiple values within a visit, the worst value will be taken (worst being the maximum value of the composite score of the vulvovaginal signs and symptoms). All analysis will be performed based on the ITT, mITT, and PP sets. The similar analyses will be performed for below 2 categorizations of the composite score of the vulvovaginal signs and symptoms: <7, >=7 and '4 - 7', '8 - 12', and '>=13'.

A listing will be provided to present the signs and symptoms score and mycological outcome for all subjects in the ITT set. Assessments that are not done will be presented in the data listing with a missing value.

Signs of VVC will be defined as the presence of erythema, edema, or excoriation. Symptoms of VVC will be defined as itching, burning, or irritation.

Each vulvovaginal sign will be objectively scored based on severity as follows:

0 = none (complete absence of any signs or symptoms);

1 = mild (slight);

2 = moderate (present);

3 = severe (marked, intense).

Each vulvovaginal symptom will be objectively scored based on severity as follows:

0 = none (I have no discomfort);

1 = mild (I have some discomfort, but it does not bother me much);

2 = moderate (I have discomfort, which is annoying, but not enough to affect what I am doing);

3 = severe (I have discomfort, which is annoying enough to affect what I am doing).

The composite score of the vulvovaginal signs and symptoms will be calculated according to the following rules and this scale has a total possible score of 18.

- If all items of the vulvovaginal signs and symptoms have been scored, the composite score is calculated as the sum of the individual scores of all 3 items of signs and 3 items of symptoms;
- If any sign or symptom is not done, the composite score will not be calculated and treated as a missing data except at Week 4, Week 8, and Week 36 (EOFU);
- Subjects who have no suspicion of a potential recurrence are not required per protocol to have a vaginal examination at Week 4, Week 8, and Week 36 (EOFU), therefore signs are not considered missing when subjects are free of symptoms and there is not suspicion of a potential recurrence. For subjects who do not present symptoms and have no suspicion of a potential recurrence at Week 4, Week 8, and Week 36 (EOFU), the total sign score and the composite score of the vulvovaginal signs and symptoms at Week 4, Week 8, and Week 36 (EOFU) will be calculated as zero. Otherwise, the composite score will not be calculated and treated as a missing.

9. Safety Analysis

Safety analyses will be performed on all subjects in the safety set, unless otherwise specified. Analyses will be based on adverse events, vital signs, clinical laboratory assessments, and abbreviated physical examination findings. Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics by treatment group.

Individual subject listings will be provided to support the tables.

9.1. Adverse Events

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.

A prior adverse event (PAE) is defined as adverse event whose start date is before the date of the first dose of study treatment. For subjects who didn't take study treatment, all AEs will be identified as PAE. A Summary of the total number of PAE and the number and percentage of subjects with at least one PAE will be provided by SOC and PT based on all screened patients. Besides, a subject listing will be presented for all the prior adverse events.

A TEAE is defined as any event does not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug.

For the purpose of inclusion in TEAE tables, incomplete AE start and end dates will be imputed as follows:

Incomplete onset dates (where UK and UNK indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: If the month and year are different from the month and year of the date of first dose, assume 01-MMM-YYYY. If the month and year are the same as the month and year for the date of first dose, and the end date (after any imputation) is on or after the date of first dose, then assume the date of first dose. If the month and year are the same as the date of first dose, and the end date (after any imputation) is prior to the date of first dose, then assume the end date for the start date.
- DD-UNK-YYYY/UK-UNK-YYYY: If the year is different from the year of the date of first dose, assume 01-JAN-YYYY of the collected year. If the year is the same as the date of first dose year, and the end date (after any imputation) is on or after the date of first dose, then assume the date of first dose. If the year is the same as the date of first dose, and the end date (after any imputation) is prior to the date of first dose, then assume the end date for the start date.

Incomplete end dates (where UK and UNK indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: Assume the last day of the month;
- DD-UNK-YYYY/UK-UNK-YYYY: Assume 31-DEC-YYYY.

The missing onset dates will be imputed as the date of first dose of study drug. The missing end date will be imputed as the subject's last visit date.

All adverse events will be classified by SOC and PT according to the Medical Dictionary for Regulatory Activities (MedDRA, Version 19.1 or higher).

An overview summary of the number and percentage of subjects with any TEAE, serious TEAE, treatment-related TEAE, treatment-related serious TEAE, TEAE leading to study treatment discontinuation, TEAE leading to study discontinuation, and AE leading to death will be provided by treatment group and study period (prior or on TOC visit, after TOC visit but prior or on EOFU visit, and entire study).

All AEs will be presented in a listing.

9.1.1. Treatment-Emergent Adverse Events

Summaries of the total number of TEAEs and the number and percentage of subjects with at least one TEAE will be provided by treatment and study period (prior or on TOC visit, after TOC visit but prior or on EOFU visit, and entire study). Treatment-emergent AEs will be presented by SOC and PT. At each level of subject summarization, a subject is counted once if the subject reported one or more events. Percentages will be calculated out of the number of subjects in the safety set.

The summary of TEAEs will be presented in alphabetical order of SOC. Within each SOC, PTs will be sorted in descending order from the PT with the highest total frequency (that is, summed across all treatment groups) to the PT with the lowest total frequency. If the total frequency for any two or more PTs is equal, the PTs will be presented in alphabetical order.

The summarization described above will also be repeated for the following:

- Serious Adverse Events;
- Treatment-Related Adverse Events;
- Treatment-Related Serious Adverse Events;
- Adverse Events Leading to Dose Interruption.

The adverse events with a missing relationship will be considered as "Treatment Related" in the tables.

9.1.2. Relationship of Adverse Events to Study Treatment

A summary of TEAEs by relationship to study treatment will be presented in a table. The investigator will provide an assessment of the relationship of the event to the study treatment. The possible relationships are "Not Related" and "Related". In the TEAE relationship table, if subject reports multiple occurrences of the same TEAE, only the most closely related occurrence will be

presented. Treatment-emergent AEs that are missing a relationship will be presented in the summary table as "Related" but will be presented in the data listing with a missing relationship. Percentages will be calculated based on the number of subjects in the safety set.

The TEAE data will be categorized and presented by SOC, PT, and relationship in a manner similar to that described in Section 9.1.1.

Additionally, the TEAE data will be categorized and presented by SOC, PT, relationship, and duration (1 day, 2 days, >=3 days). The duration is calculated as the TEAE end date minus the TEAE start date, then add 1 day. At each combination level of relationship and duration, a subject is counted once if the subject reported one or more events. Percentages will be calculated out of the number of subjects in the safety set.

Treatment-emergent SAEs by relationship to study treatment will also be presented in a table. Treatment-emergent SAEs that are missing a relationship will be presented in the table as "Related" but will be presented in the data listing with a missing relationship.

9.1.3. Severity of Adverse Event

A summary of TEAEs by severity will be presented in a table. The severity that will be presented represents the most extreme severity captured on the CRF page. The possible severities are "Mild", "Moderate", and "Severe".

In the TEAE severity table, if a subject reported multiple occurrences of the same TEAE, only the most severe will be presented. An additional row "Missing" must be added for the missing severity. Percentages will be calculated out of the number of subjects in the safety set.

The TEAE data will be categorized and presented by SOC, PT, and severity in a manner similar to that described in Section 9.1.1.

Additionally, the TEAE data will be categorized and presented by SOC, PT, severity, and relationship. At each combination level of severity and relationship, a subject is counted once if the subject reported one or more events. Percentages will be calculated out of the number of subjects in the safety set.

Treatment-emergent SAEs by severity will also be presented in a table.

9.1.4. Adverse Events Leading to Treatment Discontinuation

A summary of the TEAEs with an action taken with study treatment of "Drug Withdrawn" will be presented by treatment in a manner similar to that described in Section 9.1.1.

Any TEAEs leading to treatment discontinuation will be presented in a listing for all subjects.

9.1.5. Adverse Events Leading to Study Discontinuation

All subjects who have an AE with the answer to "Caused Study Discontinuation" is "Yes" will be presented in a listing.

9.1.6. Death

All subjects who have an AE with an outcome of "Death Related to Adverse Event" will be presented in a listing.

9.2. Clinical Laboratory Evaluations

Summary tables will be presented for laboratory test results (hematology and blood chemistry) by treatment at Screening and the scheduled post-treatment visits for subjects in the safety set.

All relevant clinical laboratory tests in chemistry and hematology will be classified as Low, Normal, and High according to the normal ranges. This categorical data will be summarized in shift tables comparing the extreme results at post-treatment study scheduled visits with those at the baseline visit. Extreme post-baseline results will also be summarized. When there are multiple values within a visit for a particular laboratory variable, the worst value will be taken (worst being the smallest value for criteria below a certain threshold or the largest value for criteria above a certain threshold). If a subject has a value below the threshold and above the threshold, the value furthest from the threshold will be chosen.

Plots of average clinical laboratory parameters may be presented.

In data listings, laboratory values will be compared to normal ranges; out-of-range values will be identified.

9.2.1. Pregnancy

Female subjects of child-bearing potential will have urine pregnancy tests conducted at baseline (Day 1) visit and at the unscheduled visits, if needed. Only subjects with negative pregnancy test results will be enrolled. Any subjects with positive pregnancy test results at any time during the study will be presented in a listing.

9.2.2. Events of Clinical Interest

The frequency and percentage of subjects with the following elevations will be summarized at any post-baseline visit:

- ALT or AST > 8 × the upper limit of normal (ULN);
- ALT or AST > 5 × ULN for more than 2 weeks or accompanied by total bilirubin > 2 × ULN.

A listing will be provided for the above elevations, including the actual measurement of ALT, AST, and total bilirubin, and their reference high limits.

9.3. Vital Sign Measurements

Summary tables will be presented for vital sign data, including systolic blood pressure (mmHg), diastolic blood pressure (mmHg), body temperature (°C), respiratory rate (bpm), and pulse rate (bpm), by treatment for subjects in the safety set. Observed results at the scheduled visits and

changes from baseline to the scheduled post-treatment visits will be presented. All vital sign data by subject will be presented in a listing.

9.4. 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.

The abbreviated physical examinations will be classified as Normal, and Abnormal at baseline. The post-baseline examinations will be classified as "Changes from baseline" or "No change from baseline". This categorical data will be summarized with the frequency and percentage of subjects by body system at each scheduled visit.

All abbreviated physical examination data will be presented in a listing for all subjects.

9.5. Vaginal Samples – pH, KOH and Other Pathogen Results

Please refer to the section 14.7 of the protocol for the details of the Vaginal samples collection.

The KOH testing results will be classified as Positive (Yeast Only), Positive (Yeast and other pathogens), Negative (Yeast and other pathogens), and Positive (Other pathogens only). This categorical data will be summarized with the frequency and percentage of subjects at the scheduled post-baseline visits by treatment group.

The proportion of subjects with Chlamydia, Gonorrhea, and Herpes will be summarized at the scheduled visits by treatment group.

All vaginal sample testing data will be presented in a listing.

10. Interim Analysis

No interim analysis is planned for this study.

11. Changes in the Planned Analysis

The following have changed from the protocol:

- For the continuous efficacy endpoints except for the absolute number of Mycologically Proven, Presumed or Suspected Recurrences from Baseline (Day 1) to Week 24 (TOC) and Week 36 (EOFU), a Mixed-Effect Model for Repeated Measure (MMRM) analysis model and an analysis of covariance (ANCOVA) model are recommended rather than a two-way ANOVA model. Baseline value will be considered as possible contributor to any observed differences. Additionally, other variables may be considered during blinded data review.
- Add the randomization stratification factor, uncontrolled diabetes mellitus (Yes or No), as justification factor in the efficacy analyses models.

- For efficacy analyses, Country is recommended rather than site to be used as the justification factor.
- In protocol, it stated that the safety and tolerability as measured by AEs, vital signs, treatment discontinuation and safety laboratory tests at TOC (Week 24). The texts "at TOC (Week 24)" is removed since all safety data captured in this study will be taken into account for analysis.
- Intent-to-treat (ITT) Set definition was changed to be "All randomized subjects who signed the consent form and received at least one dose of study drug (ibrexafungerp or placebo)."
- Modified Intent-to-treat (mITT) Set definition was changed to be "All randomized subjects who signed the consent form and received at least one dose of study drug (ibrexafungerp or placebo), who have a confirmed mycological culture for yeast at Screening and a negative culture for yeast at Baseline (Day 1)."
- The number of recurrence episodes will be classified to 4 order categories for analysis rather than 3 categories as mentioned in the protocol. Updated based on client's request.

12. References

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13. Appendices

13.1. Appendix 1: Schedule of Assessments

	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	
Subject diary completion		X----------X			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

	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)**	
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.

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

	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)**	

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 **Error! Reference source not found.** [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 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)

13.2. Appendix 2: Standard EQ-5D-5L Value Sets

An EQ-5D summary index is derived by applying a formula that attaches values (weights) to each of the levels in each dimension. The index is calculated by deducting the appropriate weights from 1, the value for full health. Below is a part of the value sets for your reference. The full value sets used for this study will be saved in a excel file and used as an external data to import into the study database for EQ-5D index value selection.

Health State	**Country/Region**			
5L Profile	**Russia**	**Poland**	**USA**	**Bulgaria**
11111			1.000	
11112			0.876	
11113			0.844	
11114			0.700	
11115			0.550	
11121			0.861	
11122			0.820	
11123			0.809	
11124			0.669	
11125			0.524	
11131			0.827	
11132			0.806	
11133			0.800	
11134			0.661	
11135			0.517	
11141			0.682	
……				

13.3. Appendix 3: SF-36 SCORING ALGORITHM

The SF-36 is a validated generic QOL questionnaire that measures 8 health dimensions: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. The General Health question will be examined, and two overall scores will be calculated. The Physical Health summary measure is an aggregate of the physical functioning, role-physical, bodily pain and general health scales. The Mental Health summary measure is an aggregate of the vitality, social functioning, role-emotional, and mental health scales. The SF-36 demonstrates acceptable validity and reliability and has been used in osteoarthritis (OA), low back pain, and cancer pain.

The SF-36 consists of 11 sections. Some of the sections consist of multiple items. To specify scoring formulas, the 11 sections will be denoted by Question 1 to Question 11 according to the order in the questionnaire; and the individual items by their alphabetic order. For example, the first item in section 3 is represented as Question 3a.

Each item on the 36-item short-form health survey (SF-36) will be answered by a patient. Some of the answers will then be re-coded so that across all questions, a higher score will indicate a better health state. Question 2 (Compared to one year ago, how would you rate your health in general now) is not used in the calculation of domain scores. Questions 3, 4, 5, 9b, 9c, 9f, 9g, 9i, 10, 11a, 11c will be scored as recorded; the other scores will be transformed as follows:

- Question 1:

Original Response	1	2	3	4	5
Re-coded Response	5	4.4	3.4	2	1

- Questions 6, 9a, 9d, 9e, 9h, 11b, 11d:

Original Response	1	2	3	4	5
Re-coded Response	5	4	3	2	1

- Question 7:

Original Response	1	2	3	4	5	6
Re-coded Response	6	5.4	4.2	3.1	2.2	1

- Question 8 (if question 7 is answered):

Original Response to #8	1	1	2	3	4	5
Original Response to #7	1	2-6	1-6	1-6	1-6	1-6
Re-coded Response	6	5	4	3	2	1

- Question 8 (if question 7 is NOT answered):

Original Response	1	2	3	4	5
Re-coded Response	6	4.75	3.5	2.25	1

The raw score for the following 8 domains will be calculated by summing the re-coded scores for the set of questions listed in the table below if all of the questions within that domain are answered. If < 50% of the questions within a domain are answered, the raw score will not be calculated.

Domain	**Questions**
Physical functioning	3a-3j
Role limitations due to physical health	4a-4d
Bodily pain	7-8
General health	1, 11a-d
Vitality	9a, 9e, 9g, 9i
Social functioning	6, 10
Role limitations due to emotional problems	5a – 5c
Mental health	9b, 9c, 9d, 9f, 9h

If ≥50% but not all of the questions are answered, the non-missing questions are re-coded (if necessary, per above) and then summed. An average score is calculated for those non-missing scores and that average score is imputed as the score to be used for the value of the missing questions. The raw score is then calculated as the sum of all of the question scores. For example, for the vitality domain, if questions 9a, 9e, and 9g are answered but question 9i is missing, the algorithm will proceed as follows from left to right:

Question	Patient-Recorded Response	Response after Re-coding	Average of non-missing scores = (4+2+5)/3 =3.6666…	Average imputed for missing responses	Raw Score = 4+2+5+3.6666 = 14.6666
9a	2	4		4	
9e	4	2		2	
9g	5	5		5	
9i	Missing	Missing		3.6666…	

After the raw score is calculated, the raw score is converted into a normalized score (on a scale of 0 to 100) using the following transformation:

$$\text{Normalized score} = \frac{(\text{Raw Score} - \text{Lowest Possible Raw Score}) \times 100}{\text{Possible Raw Score Range}}$$

The normalized domain scores will then be standardized using means and SDs from the 1998 general U.S. population by the following formula:

$$\text{Standardized score} = \frac{\text{Normalized Score} - a}{b}$$

The lowest possible raw score, possible raw score range, (a) mean values and (b) SDs values from the 1998 general U.S. population for each domain are as follows:

Domain	Lowest Possible Raw Score	Possible Raw Score Range	a	b
Physical functioning	10	20	83.29094	23.75883
Role limitations due to physical health	4	16	82.50964	25.52028
Bodily pain	2	10	71.32527	23.66224
General health	5	20	70.84570	20.97821
Vitality	4	16	58.31411	20.01923
Social functioning	2	8	84.30250	22.91921
Role limitations due to emotional problems	3	12	87.39733	21.43788
Mental health	5	20	74.98685	17.75604

The two raw component scores will be calculated based on multiplying each standardized domain score by a weights (factor score coefficients) derived from the 1990 general U.S. population, and then adding the 8 domains together. The constants to use for the two component scores are as follows:

Domain	Physical Component Summary	Mental Component Summary
Physical functioning	0.42402	-0.22999
Role limitations due to physical health	0.35119	-0.12329
Bodily pain	0.31754	-0.09731
General health	0.24954	-0.01571
Vitality	0.02877	0.23534
Social functioning	-0.00753	0.26876
Role limitations due to emotional problems	-0.19206	0.43407
Mental health	-0.22069	0.48581

The norm-based scores for the two component summaries will then be calculated by multiplying the raw component score by 10 and adding 50.

The norm-based scores for the 8 domains will be calculated by multiplying the standardized domain score by 10 and adding 50.

The norm-based scores will be used in the analyses.

13.4. Appendix 4: SAP for the Nested Sub-Study SCY-078-304S

13.4.1. 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.

13.4.2. Objectives

13.4.2.1. Primary 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 Clinical Success.

13.4.2.2. 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.

13.4.3. Investigational Plan

13.4.3.1. Overall Study Design and Plan

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 a Baseline visit on Day 1, a TOC visit on Day 11 (±3) and a FU visit on Day 25 (±4).

The schedule of study assessments is presented in Appendix S1.

13.4.3.2. Study Endpoints

13.4.3.2.1. Primary Endpoints

- 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.

13.4.3.2.2. Secondary Efficacy 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;
- Physical examination;
- Treatment discontinuation;
- Safety laboratory tests.

13.4.3.3. Treatments

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

13.4.4. General Statistical Considerations

Please refer to Section 4 of the main study above for the details of general statistical considerations.

13.4.4.1. Sample Size

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.

13.4.4.2. Randomization, Stratification and Blinding

This is an open-label, single-group study. There will be no study-drug blinding, randomization or stratification.

13.4.4.3. Analysis Set

Intent-to-Treat (ITT) Set: All ibrexafungerp-treated subjects.

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

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

13.4.4.4. Handing of missing data

For categorical response endpoints including clinical outcome, mycological outcome, symptom outcome, and clinical improvement, subjects will be considered a non-responder for the non-responder imputation (NRI) analysis if they are missing categorical response data at the specific visit. Randomized subjects without at least 1 post-baseline observation will also be defined as non-responder for the NRI analysis such that subjects who have a missing value at the TOC visit or FU visit will be assigned as treatment failures, i.e., non-responders or positive mycological outcome for the corresponding visit. Randomized subjects without study treatment will be excluded from all analysis.

13.4.5. Subject Disposition

13.4.5.1. Disposition

A disposition of subjects includes the number and percentage of subjects for the following categories: subjects in each analysis set (ITT, mITT, SS), subjects who completed TOC visit, subjects who completed the study, subjects who discontinued from the study, and the reasons for study discontinuation will be presented by the ITT and mITT sets. All percentages will be based on the number of subjects in each corresponding set.

The reason for study discontinuation may include any of the following: Absence of culture-confirmed Candida spp. infection from the sample reviewed at Baseline, Adverse Event, Lost to Follow-up, Physician Decision, Pregnancy, Study Terminated by Sponsor, Withdrawal by Parent or Guardian, Withdrawal by Subject, Other, Death, Trial Screen Failure.

Subject disposition data will be presented in a listing.

13.4.5.2. Protocol Deviations

The investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate IRB, except when necessary to eliminate immediate hazards to the subject or when the change(s) involve(s) only logistical or administrative aspects of the study.

Significant protocol deviations will be defined in the significant protocol deviations rules document. Each significant deviation will be assigned a rule number. As the study is ongoing, additional significant protocol deviations can also be spontaneously identified or defined by the sponsor and/or the project team during the regularly planned study deviation review meetings and the significant protocol deviations rules document can be updated.

All protocol deviations will be reviewed and assessed as to significance prior to the database lock. The list of protocol deviations (significant or minor) that are additionally considered major clinically relevant for the purposes of analysis will also be identified prior to the database lock.

All major protocol deviations (i.e. resulting in exclusion of the subjects from one or more analysis) will be summarized using the ITT and mITT sets.

Major protocol deviations will also be presented in a listing.

13.4.6. Demographics and Baseline Characteristics

13.4.6.1. Demographics

A summary of the following demographics will be presented for the subjects in ITT set and mITT set, respectively.

- Age (years);
- Age group (<18 years, 18 -<36 years, 36 -<50 years, 50 -<65 years, >=65 years);
- Sex (Female);
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and Other);
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino);
- Country [USA (United States), BGR (Bulgaria), RUS (Russia), POL (Poland)];
- Geographical location (USA, EX-USA);
- BMI (kg/m²);
- BMI group (Underweight <18.5 kg/m², Normal 18.5-<25 kg/m², Overweight 25-<30 kg/m², Obese 30-<40 kg/m² and Morbidly Obese ≥40 kg/m²);
- BMI group (≤35 kg/m² and >35 kg/m²).

The age collected in CRF will be used for analysis if it is non-missing. If the age is not collected in the CRF, the age in years is calculated using the date of the informed consent and date of birth.

$$\text{Age (years)} = [(\text{Informed Consent Date} - \text{Date of Birth} + 1) / 365.25].$$

BMI is calculated as

$$\text{BMI} = (\text{body weight in kilograms}) / (\text{height in meters})^2.$$

Demographics for all subjects in the ITT set will be presented in a listing.

13.4.6.2. Baseline Characteristics

A summary of the following baseline characteristics will be presented for subjects in the ITT and mITT sets, respectively.

- Number of recurrent VVC episodes in the prior year;
- Uncontrolled diabetes mellitus (Yes or No);
- Candida species at screening (by Genus species);
- Candida species at baseline (by Genus species);
- Composite score of the vulvovaginal signs and symptoms at screening;

- Severity of VVC at screening (the composite score of the vulvovaginal signs and symptoms at screening '4 - 7', '8 - 12', and '>=13');
- Severity of VVC at screening (the composite score of the vulvovaginal signs and symptoms at screening <7, >=7);
- Fertility Status (Surgically Sterile/Infertile; Post-Menopausal; Potentially Able to Bear Children);
- Method of Birth Control (Barrier Methods Only; Oral Contraceptives; Depo Contraceptives (Implants/Injectables); IUD; Abstinence; Vaginal Ring; Vasectomized Partner; None; Other);

A separate summary table will be presented to include MIC range, mode, MIC50, and MIC90, based on the mITT set by treatment and geographical region (USA or Ex-USA) for the following MIC results from 2 different methods, CLSI and EUCAST, respectively:

- MIC results for SCY-078 and fluconazole (FLU) at 24 hours against candida species isolates obtained at Baseline;
- MIC results for SCY-078 and fluconazole (FLU) at 48 hours against candida species isolates obtained at Baseline.

Baseline characteristics for all subjects in ITT set will be presented in a listing.

13.4.6.3. Medical History

Medical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA; Version 19.1 or higher). A frequency summary (number and percentage) of subjects with at least one medical history will be presented by system organ class (SOC), and preferred term (PT), with SOCs sorted in alphabetical order and PTs within each SOC in descending order of frequency for all subjects in the ITT and mITT sets.

In addition, A summary of other vulvovaginal conditions (Selected SOC and Preferred Terms) will be presented by system organ class (SOC), and preferred term (PT) for subjects in the mITT set.

A by-subject listing of medical history will be provided.

13.4.6.4. Inclusion and Exclusion Criteria

Prior to enrollment, the investigator will assess if the subject fulfills all of the inclusion and none of the exclusion criteria outlined in the protocol (sections 21.3.7.1 and 21.3.7.2). The specific inclusion criterion not met or exclusion criterion which was met will be recorded in the eCRF.

13.4.7. Treatments and Medications

13.4.7.1. Prior and Concomitant Medications

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

For the purpose of inclusion in prior and/or concomitant medication tables, incomplete medication start and stop dates will be imputed as follows:

Missing start dates (where UK, UKN and UNKN indicate unknown or missing day, month and year respectively):

- UK-MMM-YYYY: Assume 01-MMM-YYYY. If the month and year are the same as the first dose of study drug month and year, then assume the date of first dose of study drug;
- UK-UKN-YYYY: If the year is prior to the year of first dose of study drug, assume 01-JAN-YYYY of the collected year. If the year is the same as the first dose of study drug year, then assume the date of first dose of study drug;
- UK-UKN- UNKN: Assume date of first dose of study drug.

Missing stop dates for concomitant medications data will be handled as follows (where UK, UKN and UNKN indicate unknown or missing day, month and year respectively):

- UK-MMM-YYYY: Assume the last day of the month;
- UK-UKN-YYYY: Assume 31-DEC-YYYY;
- UK-UKN- UNKN: Assume ongoing and leave it missing.

All prior and concomitant medications will be coded using the current version of the World Health Organization Drug Dictionary Enhanced (WHO-DD) and summarized by treatment group based on the ITT and mITT sets.

13.4.7.1.1. Prior Medications

Prior medications are defined as medications taken and stopped prior to the first dose of study drug. The number and percentage of subjects who took prior medications will be presented by WHO therapeutic drug class and generic drug name.

In addition, a summary of the following will be presented for subjects in the mITT set:

- Antibiotic use 30 days before baseline visit;
- Systemic steroid use 30 days before baseline visit.

13.4.7.1.2. Concomitant Medications

Concomitant medications are defined as medications started on or before the FU visit date with missing stop dates or stop dates after the first dose of study drug.

A summary showing the number and percentage of subjects who took concomitant medications will be presented by WHO therapeutic drug class and generic drug name.

A by-subject listing of prior and concomitant medications will be provided.

13.4.7.1.3. Rescue Antifungal Medications

The number and percentage of subjects who took rescue antifungal medication, prior or on TOC, after TOC but before FU, at FU visit will be presented for the ITT and mITT sets.

A by-subject listing of rescue antifungal medications will be provided.

13.4.7.2. Study Treatments

Please refer to Section 13.4.3.3 for the details of the study treatment.

Data related to the study treatment will be presented in a listing.

13.4.7.2.1. Study Participation Calculation and Extent of Exposure

The duration of study treatment (hours) is calculated as (the date time of the second dose – the date time of the first dose + 1) / 3600 only for subjects who got both 2 study treatments. For subjects who only got 1 or none study treatment, the duration of study treatment will be missing.

The duration of study participation (days) is calculated as date of Study Completion/Termination recorded on the End of Study page – first dose date + 1. If the date of Study Completion/Termination on the End of Study page is missing, or if a subject is lost to follow-up, the latest available visit date will be used.

The cumulative doses taken across the treatment period is defined as the number of study drug dispensed minus the number of study drug returned. If the study drug bottle was not returned, the dose diary data will be considered for the cumulative dose calculation. When subject answered no dose missing, we can assume the cumulative dose is 4. When subject answered only 1 dose missing, we can assume the cumulative dose is 2. When subject answered 2 doses missing, we can assume the cumulative dose is 0 tablet. The cumulative dose is missing when subject didn't answer at least one missing dose question.

The duration of study participation, the number of drug administrations and the cumulative doses by treatment will be summarized by summary statistics.

All this exposure information will be presented in a listing.

13.4.7.2.2. Treatment Compliance

Treatment compliance is defined as the ratio of total study dose to the planned dose, in terms of percentage. Treatment compliance will be summarized descriptively.

Treatment compliance = the cumulative dose / the planned dose (4 tablets) *100%.

The treatment compliance will be classified as 0, 25%, 50%, 75%, and 100%. This categorical data will be summarized with the frequency and percentage of subjects.

Non-compliance with dose regimen (example all four tablets taken as a single dose) will be captured based on investigator's review of subject diary.

13.4.8. Efficacy Analysis

The primary efficacy and secondary efficacy endpoints will be performed on the modified intent-to-treat set (mITT), and the intent-to-treat set (ITT). The mITT analyses will be considered primary; the ITT analyses will be considered supportive of the primary analyses on the mITT population. The denominator for all percentages will be the number of subjects in that treatment within the analysis set of interest, unless otherwise specified.

13.4.8.1. Primary Endpoint

The primary efficacy endpoint is defined as 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.

Clinical success will be assessed at the TOC Visit (Day 11) according to the following definitions:

- 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 prior to or at the TOC visit;
- Clinical failure: less than 50% reduction from baseline in the total composite VSS score or need for additional antifungal therapy. For the subject who early terminated before TOC visit and received additional vulvovaginal or systemic antifungal therapy or topical vaginal drug therapy for the treatment of vulvovaginal irritation/pruritus prior to or at the early termination visit, the subject is considered a clinical failure.

Signs of VVC will be defined as the presence of erythema, edema, or excoriation. Symptoms of VVC will be defined as itching, burning, or irritation.

Each vulvovaginal sign will be objectively scored based on severity as follows:

0 = none (complete absence of any signs or symptoms);

1 = mild (slight);

2 = moderate (definitely present);

3 = severe (marked, intense).

Each vulvovaginal symptom will be objectively scored based on severity as follows:

0 = none (I have no discomfort);

1 = mild (I have some discomfort, but it does not bother me much);

2 = moderate (I have discomfort, which is annoying, but not enough to affect what I am doing);

3 = severe (I have discomfort, which is annoying enough to affect what I am doing).

The composite score of the vulvovaginal signs and symptoms will be calculated according to the following rules and this scale has a total possible score of 18.

- If all items of the vulvovaginal signs and symptoms have been scored, the composite score is calculated as the sum of the individual scores of all 3 items of signs and 3 items of symptoms;
- If any sign or symptom is not done, the composite score will not be calculated and treated as a missing data except at FU visit;
- Subjects who are free of symptoms are not required per protocol to have a vaginal examination at FU visit, therefore signs are not considered missing. For subjects who do not present symptoms and have no sign rated at the FU visit, the composite score of the vulvovaginal signs and symptoms at the FU visit will be calculated as zero.

13.4.8.1.1. Primary Analysis

The primary efficacy analysis will be performed on the mITT set at the TOC visit. The number and percentage of subjects with clinical success at the TOC visit will be presented. The 95% confidence interval of the clinical success rate will be calculated using the method of Clopper and Pearson. Missing data for clinical outcome will be imputed using the NRI method described in Section 13.4.4.4. Additional summarizations will be performed by Candida Species of the baseline yeast, but not subject to formal statistical analysis.

The same analysis employing the same methods as for the primary analysis will be performed for the ITT set to assess clinical success at TOC visit. Missing data for clinical outcome will be imputed using the NRI method described in Section 13.4.4.4.

A sensitivity analysis using the mITT set will be performed where subjects with the imputed clinical outcome using the NRI method at TOC visit will be removed from the analysis.

Summary of the number and percentage of subjects with continued clinical success at the Follow-up (FUP) visit, which defined as continued clinical success in subjects who achieved Clinical Success at the TOC visit, will be provided based on the ITT, and mITT sets.

13.4.8.2. Secondary Efficacy Endpoints

13.4.8.2.1. Clinical Outcome – Clinical Cure

A summary with the number and percentage of subjects with clinical cure at the TOC visit will be presented by Candida Species of the baseline yeast and overall. Clinical outcomes will be assessed at the TOC Visit (Day 11) according to the following definitions:

- Clinical cure: Complete resolution of signs and symptoms of vulvovaginal infection without need for further antifungal treatment and topical vaginal drug therapy for the treatment of vulvovaginal irritation/pruritus prior to or at the TOC visit. Specifically, for complete resolution, any sign or symptom should be absent (score = 0);
- Not clinical cure: No response to therapy or incomplete resolution of signs and symptoms or use of additional vulvovaginal or systemic antifungal therapy or topical vaginal drug

therapy for the treatment of vulvovaginal irritation/pruritus prior to or at the TOC visit. For the subject who early terminated before TOC visit and received additional vulvovaginal or systemic antifungal therapy or topical vaginal drug therapy for the treatment of vulvovaginal irritation/pruritus prior to or at the early termination visit, the subject is considered a not clinical cure.

13.4.8.2.2. Mycological outcomes

A summary with the number and percentage of subjects with mycological eradication (negative culture for growth of Candida species) at the TOC visit will be performed by Candida species of the baseline yeast and overall. The subjects with missing TOC visit data for the mycological outcome will be imputed as mycological persistence using the NRI method described in Section 13.4.4.4.

Mycological outcomes will be assessed at the specified visit according to the following definitions.

- Mycological Eradication: A subject with negative culture for Candida species without need for further antifungal treatment prior to the TOC visit. For subjects who are free of symptoms and have no vulvovaginal specimens obtained at the TOC visit, the subject will be considered as mycological eradication;
- Mycological Persistence: A subject with a positive culture for Candida species or use of additional vulvovaginal or systemic antifungal therapy prior to the TOC visit. For the subject who early terminated before TOC visit and received additional vulvovaginal or systemic antifungal therapy prior to the early termination visit, the subject is considered a mycological persistence.

The same analysis will be done for the percentage of subjects with mycological eradication (negative culture for growth of Candida species) at the FU visit. For subjects who are free of symptoms and have no vulvovaginal specimens obtained at the FU visit, the subject will be considered as mycological eradication at the FU visit.

The change of mycological outcomes will be summarized in shift tables comparing the testing results at TOC visit with those at FU visit.

The analyses for mycological outcome will only be conducted for the mITT set.

In addition, a summary table will be presented to include MIC range, mode, MIC50, and MIC90, based on the ITT and mITT sets by treatment group and geographical region (USA or Ex-USA) for the following MIC results from 2 different methods, CLSI and EUCAST, respectively:

- MIC results for SCY-078 and fluconazole (FLU) at 24 hours against candida species isolates obtained at TOC visit;
- MIC results for SCY-078 and fluconazole (FLU) at 48 hours against candida species isolates obtained at TOC visit.

Frequency cross-tabulations of mycological persistence at baseline versus mycological eradication at TOC visit will be presented by treatment group by candida species isolates obtained at baseline based on mITT set.

13.4.8.2.3. Overall Outcome

A summary with the number and percentage of subjects with clinical cure and mycological eradication (overall outcome) at the TOC visit will be performed by Candida Species of the baseline yeast and overall. The subjects who cannot determine the overall outcome at the TOC visit will be removed from the analysis and no missing data will be imputed for both clinical outcome and mycological outcome.

Overall outcomes will be assessed at the TOC Visit (Day 11) according to the following definitions:

- Overall Success: A subject with the achievement of both a clinical cure and mycological eradication;
- Overall Failure: A subject with either not clinical cure or mycological persistence.

The analyses for overall outcome will only be conducted for the mITT set. The overall outcomes will be listed with baseline species referenced aside in a listing.

13.4.8.2.4. Symptom Outcome

A summary with the number and percentage of subjects with complete resolution of symptoms at the Follow-up (FUP) visit will be performed by Candida Species of the baseline yeast and overall. The subjects with missing Follow-Up data for the symptom outcome will be imputed as symptom persistence using the NRI method described in Section 13.4.4.4.

Symptom outcomes will be assessed at the FU Visit according to the following definitions:

- Symptom Resolution: All symptoms are absent (score = 0) without need for further antifungal treatment or topical vaginal drug therapy for the treatment of vulvovaginal irritation/pruritus prior to or at FU visit;
- Symptom Persistence: No response to therapy or incomplete resolution of symptoms or use of additional vulvovaginal or systemic antifungal therapy or topical vaginal drug therapy for the treatment of vulvovaginal irritation/pruritus prior to or at FU visit. For the subject who early terminated before the FU visit and received additional vulvovaginal or systemic antifungal therapy or topical vaginal drug therapy for the treatment of vulvovaginal irritation/pruritus prior to or at the early termination visit, the subject is considered a symptom persistence.

13.4.8.2.5. Clinical Improvement

A summary with the number and percentage of subjects with clinical improvement (partial or complete resolution of signs and symptoms with total composite score no greater than 1 without need for further antifungal treatment and topical vaginal drug therapy for the treatment of vulvovaginal irritation/pruritus prior to or at TOC visit) at the TOC visit will be performed. For the subject who early terminated before the TOC visit and received additional vulvovaginal or systemic antifungal therapy or topical vaginal drug therapy for the treatment of vulvovaginal irritation/pruritus prior to or at the early termination visit, the subject is considered no clinical improvement. The subjects with missing TOC visit data for clinical improvement outcome will be imputed as no clinical improvement using the NRI method described in Section 13.4.4.4. The composite score will be calculated as the rules described in Section 13.4.8.1.

13.4.8.2.6. Composite Score of the Vulvovaginal Signs and Symptoms

The composite score of the vulvovaginal signs and symptoms and Change from Baseline values to test of cure visit and follow up visit will be summarized by treatment and by visit descriptively.

The composite score of the vulvovaginal signs and symptoms will be classified as ‘0’, ‘1’, ‘2’, and ‘>=3’. This categorical data will be summarized with the frequency and percentage of subjects at each scheduled visit. When there are multiple values within a visit, the worst value will be taken (worst being the maximum value of the composite score of the vulvovaginal signs and symptoms). All analysis will be performed based on the ITT and mITT sets. The similar analyses will be performed for below 2 categorizations of the composite score of the vulvovaginal signs and symptoms: <7, >=7 and ‘4 - 7’, ‘8 - 12’, and ‘>=13’.

A listing will be provided to present the signs and symptoms score and mycological outcome for all subjects in the ITT set. Assessments that are not done will be presented in the data listing with a missing value.

13.4.9. Safety Analysis

Safety analyses will be performed on all subjects in the safety set. Analyses will be based on adverse events, vital signs, clinical laboratory assessments, and physical examination findings. Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics.

Individual subject listings will be provided to support the tables.

13.4.9.1. Adverse Events

All AE summaries will be restricted to treatment-emergent AEs (TEAEs) only. A TEAE is defined as any event does not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug.

For the purpose of inclusion in TEAE tables, incomplete AE start and end dates will be imputed as follows:

Incomplete onset dates (where UK and UNK indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: If the month and year are different from the month and year of the date of first dose, assume 01-MMM-YYYY. If the month and year are the same as the month and year for the date of first dose, and the end date (after any imputation) is on or after the date of first dose, then assume the date of first dose. If the month and year are the same as the date of first dose, and the end date (after any imputation) is prior to the date of first dose, then assume the end date for the start date.
- DD-UNK-YYYY/UK-UNK-YYYY: If the year is different from the year of the date of first dose, assume 01-JAN-YYYY of the collected year. If the year is the same as the date of first dose year, and the end date (after any imputation) is on or after the date of first dose, then assume the date of first dose. If the year is the same as the date of first dose, and the end date (after any imputation) is prior to the date of first dose, then assume the end date for the start date.

Incomplete end dates (where UK and UNK indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: Assume the last day of the month;
- DD-UNK-YYYY/UK-UNK-YYYY: Assume 31-DEC-YYYY.

The missing onset dates will be imputed as the date of first dose of study drug. The missing end date will be imputed as the subject's last visit date.

All adverse events will be classified by SOC and PT according to the Medical Dictionary for Regulatory Activities (MedDRA, Version 19.1 or higher).

An overview summary of the number and percentage of subjects with any TEAE, serious TEAE, treatment-related TEAE, treatment-related serious TEAE, TEAE leading to study treatment discontinuation, TEAE leading to study discontinuation, and AE leading to death will be provided by treatment group.

All AEs will be presented in a listing.

13.4.9.1.1. Treatment-Emergent Adverse Events

Summaries of the total number of TEAEs and the number and percentage of subjects with at least one TEAE will be provided. Treatment-emergent AEs will be presented by SOC and PT. At each level of subject summarization, a subject is counted once if the subject reported one or more events. Percentages will be calculated out of the number of subjects in the safety set.

The summary of TEAEs will be presented in alphabetical order of SOC. Within each SOC, PTs will be sorted in descending order from the PT with the highest total frequency (that is, summed across all treatment groups) to the PT with the lowest total frequency. If the total frequency for any two or more PTs is equal, the PTs will be presented in alphabetical order.

The summarization described above will also be repeated for the following:

- Serious Adverse Events;
- Treatment-Related Adverse Events;
- Treatment-Related Serious Adverse Events;
- Adverse Events Leading to Dose Interruption.

The adverse events with a missing relationship will be considered as “Treatment Related” in the tables.

13.4.9.1.2. Relationship of Adverse Events to Study Treatment

A summary of TEAEs by relationship to study treatment will be presented in a table. The investigator will provide an assessment of the relationship of the event to the study treatment. The possible relationships are “Not Related” and “Related”. In the TEAE relationship table, if subject reports multiple occurrences of the same TEAE, only the most closely related occurrence will be presented. Treatment-emergent AEs that are missing a relationship will be presented in the summary table as “Related” but will be presented in the data listing with a missing relationship. Percentages will be calculated based on the number of subjects in the safety set.

The TEAE data will be categorized and presented by SOC, PT, and relationship in a manner similar to that described in Section 9.1.1.

Treatment-emergent SAEs by relationship to study treatment will also be presented in a table. Treatment-emergent SAEs that are missing a relationship will be presented in the table as “Related” but will be presented in the data listing with a missing relationship.

13.4.9.1.3. Severity of Adverse Event

A summary of TEAEs by severity will be presented in a table. The severity that will be presented represents the most extreme severity captured on the CRF page. The possible severities are "Mild", "Moderate", and "Severe".

In the TEAE severity table, if a subject reported multiple occurrences of the same TEAE, only the most severe will be presented. An additional row "Missing" must be added for the missing severity. Percentages will be calculated out of the number of subjects in the safety set.

The TEAE data will be categorized and presented by SOC, PT, and severity in a manner similar to that described in Section 9.1.1.

Additionally, the TEAE data will be categorized and presented by SOC, PT, severity, and relationship. At each combination level of severity and relationship, a subject is counted once if the subject reported one or more events. Percentages will be calculated out of the number of subjects in the safety set.

Treatment-emergent SAEs by severity will also be presented in a table.

13.4.9.1.4. Adverse Events Leading to Treatment Discontinuation

A summary of the TEAEs with an action taken with study treatment of "Drug Withdrawn" will be presented by treatment in a manner similar to that described in Section 9.1.1.

Any TEAEs leading to treatment discontinuation will be presented in a listing for all subjects.

13.4.9.1.5. Adverse Events Leading to Study Discontinuation

All subjects who have an AE with the answer to "Caused Study Discontinuation" is "Yes" will be presented in a listing.

13.4.9.1.6. Death

All subjects who have an AE with an outcome of "Death Related to Adverse Event" will be presented in a listing.

13.4.9.2. Clinical Laboratory Evaluations

Summary tables will be presented for laboratory test results (hematology and blood chemistry) at Screening and TOC visit for subjects in the safety set.

All relevant clinical laboratory tests in chemistry and hematology will be classified as Low, Normal, and High according to the normal ranges. This categorical data will be summarized in shift tables comparing the extreme results at TOC visit with those at the screening visit. Extreme post-baseline results will also be summarized. When there are multiple values within a visit for a particular laboratory variable, the worst value will be taken (worst being the smallest value for criteria below a certain threshold or the largest value for criteria above a certain threshold). If a

subject has a value below the threshold and above the threshold, the value furthest from the threshold will be chosen.

Plots of average clinical laboratory parameters may be presented.

In data listings, laboratory values will be compared to normal ranges; out-of-range laboratory values will be identified.

13.4.9.2.1. Pregnancy

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

13.4.9.2.2. Events of Clinical Interest

The frequency and percentage of subjects with the following elevations will be summarized at any post-baseline visit:

- ALT or AST > 8 × the upper limit of normal (ULN);
- ALT or AST > 5 × ULN for more than 2 weeks or accompanied by total bilirubin > 2 × ULN.

A listing will be provided for the above elevations, including the actual measurement of ALT, AST, and total bilirubin, and their reference high limits.

13.4.9.3. Vital Sign Measurements

Summary tables will be presented for vital sign data, including systolic blood pressure (mmHg), diastolic blood pressure (mmHg), body temperature (°C), respiratory rate (bpm), and pulse rate (bpm), for subjects in the safety set. Observed results at the scheduled visits and changes from baseline to the TOC visit will be presented. All vital sign data by subject will be presented in a listing.

13.4.9.4. Physical Examination

The abbreviated physical examinations will be conducted at Screening and at the TOC visit.

The abbreviated physical examination comprises a routine medical examination including general appearance and an overall examination of body systems.

All abbreviated physical examinations will be classified as Normal, and Abnormal at baseline. For post-baseline examinations will be classified as “Changes from baseline” or “No change from baseline”. This categorical data will be summarized with the frequency and percentage of subjects by body system at each scheduled visit.

All abbreviated physical examination data will be presented in a listing for all subjects.

13.4.9.5. Vaginal Samples – pH, KOH and Other Pathogen Results

Vaginal samples will be obtained for pH testing, KOH testing, fungal culture, and other pathogens (Chlamydia, Gonorrhea, and Herpes) at the screening visit and other times during the study when persistence or recurrence of vulvovaginal symptoms occurs. Subjects with other pathogens other than Candida, suspected at screening will be excluded from the study.

The KOH testing results will be classified as Positive (Yeast Only), Positive (Yeast and other pathogens), Negative (Yeast and other pathogens), and Positive (Other pathogens only). This categorical data will be summarized with the frequency and percentage of subjects at the scheduled post-baseline visits.

The proportion of subjects with Chlamydia, Gonorrhea, and Herpes will be summarized at the scheduled visits.

All vaginal sample testing data will be presented in a listing.

13.4.10. Interim Analysis

No interim analysis is planned for this study.

13.4.11. Changes in the Planned Analysis

For the clinical failure definition, the texts “less than 50% reduction from baseline in the total composite VSS score” was used to replace “persistence and/or worsening of signs and symptoms” we have in the protocol.

13.4.12. Appendices – Nested Sub-study

13.4.12.1. Appendix S1: Schedule of Assessments of the Nested Sub-Study

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

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

rescheduled as soon as the subject's period ends but in no case more than 7 days after the initially 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.