SCYNEXIS, Inc.

SCY-078-303

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

16Oct, 2019

Statistical Analysis Plan

Final Version *1.0*

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List of Abbreviations

AE	adverse event
ANOVA	analysis of variance
AVVC	acute vulvovaginal candidiasis
BID	twice daily
BMI	body mass index
CFR	code of Federal Regulations
CMH	Cochran Mantel Haenszel
CRF	case report form
eCRF	electronic case report form
eDISH	evaluation of drug induced serious hepatotoxicity
FU	follow-up
ICF	Informed Consent Form
ID	identification
IRB	Institutional Review Board
ITT	intent-to-treat
IWRS	Interactive web-based response system
IVRS	interactive voice response system
KOH	potassium hydroxide
mBOCF	modified baseline observation carried forward
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
NRI	non-responder imputation
PI	principal investigator
PP	per protocol
PT	preferred term
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	system organ class
SS	safety set
TOC	test of cure
UK	unknown
UNK	unknown
VSS Scale	vulvovaginal signs and symptoms scale
VVC	vulvovaginal candidiasis

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 75% of women on at least one occasion over a lifetime.

Current treatments for VVC include topical antifungals and the use of prescription oral antifungals such a single dose of fluconazole. According to previous clinical studies, a single dose of fluconazole is able to provide an acceptable therapeutic outcome for more than half of the treated individuals, but the emergence of fluconazole resistance among *C. albicans* isolates and the frequency of cases caused by *C. glabrata*, a strain naturally less susceptible to fluconazole, signals the need for new therapeutic approaches.

Additionally, recurrence of VVC after fluconazole therapy is not uncommon and these exacerbations often involve the same microorganism identified in the initial episode, suggesting that a small number of *C. albicans* remain as a reservoir in the vagina after completion of azole therapy, becoming the source of subsequent exacerbations.

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

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 provide evidence of the efficacy and evaluate the safety of oral SCY-078 as a new class of antifungal agent with fungicidal activity against Candida spp. in the treatment of subjects with acute vulvovaginal candidiasis (AVVC).

2. Objectives

2.1. Primary Objectives

To evaluate the efficacy of oral ibrexafungerp versus placebo in subjects with AVVC by comparing the clinical outcomes of ibrexafungerp and placebo.

2.2. Secondary Objectives

- To evaluate the efficacy of oral ibrexafungerp versus placebo in subjects with AVVC based on mycological and clinical outcomes
- To evaluate the safety and tolerability of oral ibrexafungerp versus placebo in subjects with AVVC

3. Investigational Plan

3.1. Overall Study Design and Plan

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

Approximately 366 eligible subjects will be enrolled and randomized in a 2:1 ratio to either ibrexafungerp (300-mg dose twice a day [BID]) or matching placebo administered BID for 1 day. The primary objective of this study is to evaluate the efficacy of oral ibrexafungerp in subjects with AVVC by comparing the clinical outcomes of ibrexafungerp and placebo.

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

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 clinical cure (complete resolution of signs and symptoms) at the test-of-cure (TOC) visit.

3.2.2. Secondary Efficacy Endpoints

Efficacy as measured by:

- The percentage of subjects with mycological eradication (negative culture for growth of Candida species) at the TOC visit;
- The percentage of subjects with clinical cure and mycological eradication (responder outcome) at the TOC visit;

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

Safety and tolerability as measured by:

- Adverse events (AEs);
- Vital signs;
- Physical examination;
- Treatment discontinuation;
- Safety laboratory tests.

3.3. Treatments

At Baseline (Day 1), eligible subjects will be randomized in a 2:1 ratio to one of the following two treatment groups:

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

For the purpose of maintaining treatment blinding, all subjects randomized to the placebo group will receive matching ibrexafungerp placebo tablets. Subjects will receive their first dose of study drug at the site. 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.

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.

4.1. Sample Size

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

from the study, an additional 84 subjects are added for a total of 366 subjects (244 subjects randomized to ibrexafungerp and 122 subjects, to placebo).

4.2. Randomization, Stratification and Blinding

Approximately 366 eligible subjects will be enrolled and randomized in a 2:1 ratio to one of the following two study treatment groups:

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

An interactive response system (voice or web-based) 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/IVRS, which will link sequential subject randomization numbers to treatment codes. The block size 6 will be used in the randomization schedule.

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 a diagnosis of diabetes mellitus (diabetes mellitus: YES or NO).

4.3. Analysis Set

Intent-to-Treat (ITT) Set: All randomized subjects who signed the consent form and received at least one dose of study drug.

Modified Intent-to-Treat (mITT) Set: All randomized subjects who have a positive culture for Candida species at baseline and taking at least one dose of study drug.

Per-Protocol (PP) Set: All mITT subjects who meet all of the following criteria:

- Completed the study drug treatment;
- Have a TOC evaluation that includes documentation of signs, symptoms and collection of a vaginal culture;
- No major protocol deviation.

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

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 do not meet the clinical response criteria for categorical responses or 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.

5. Subject Disposition

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, PP, SS), subjects who completed TOC visit, subjects who completed the study (without need for antifungal treatment), subjects who completed the study (with need for antifungal treatment at FU visit), 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: lack of efficacy and/or use of antifungal therapy prior to TOC; use of antifungal therapy after TOC (but prior to FU visit); adverse event; lack of efficacy after TOC; lost to follow-up; physician decision; pregnancy; study terminated by sponsor; study subject withdrawal by parent or guardian; withdrawal by subject; other; death, and 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 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 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);
- BMI (kg/m^2);
- BMI group (Underweight <18.5 kg/m^2, Normal 18.5-<25 kg/m^2, Overweight 25-<30 kg/m^2, Obese 30-<40 kg/m^2 and Morbidly Obese ≥ 40 kg/m^2).
- BMI group (≤35 kg/m^2 and >35 kg/m^2).

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.

- Diabetes mellitus (Yes or No);
- Candida species at baseline (by Genus species);
- 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 CLSI MIC range, mode, MIC50, and MIC90, based on the ITT and mITT sets by treatment group for the following MIC results:

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

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 19.0 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 the following will be presented by system organ class (SOC), and preferred term (PT) for subjects in the mITT set:

- History of recurrent VVC as evidence by applicable PT;
- Other vulvovaginal conditions (Selected SOC and Preferred Terms).

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

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 11.1 and 11.2). The specific inclusion criterion not met or exclusion criterion which was met will be recorded in the eCRF. This information will be presented in a listing.

7. Treatments and Medications

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).

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 mITT set:

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

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.

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.

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. 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 actual doses by treatment will be summarized by summary statistics.

All this exposure information will be presented in a listing.

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 by treatment group.

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.

8. Efficacy Analysis

The primary efficacy and secondary efficacy endpoints will be performed on the modified intent-to-treat set (mITT), the intent-to-treat set (ITT) and the per-protocol (PP) set. The mITT analyses will be considered primary; the ITT and PP 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.

8.1. Primary Endpoint

The primary efficacy endpoint is defined as the proportion of mITT subjects who have a clinical cure (complete resolution of signs and symptoms) at the test-of-cure (TOC) visit.

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);
- Clinical failure: 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 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.

8.1.1. Primary Analysis

The primary efficacy analysis will be performed on the mITT set at the TOC visit and will compare the proportion of subjects, in the treatment and placebo groups, who have a clinical cure at the TOC visit.

The number and percentage of subjects with clinical cure at the TOC visit will be presented by treatment group. A Cochran Mantel Haenszel (CMH) test adjusted for site and diabetes mellitus diagnosis (Yes or No) will be performed to assess the statistical significance of a difference between treatment groups in the primary efficacy analysis. Mathematically stated:

H_0: TOC Clinical Cure Rate $_{\text{Oral ibrexafungerp 300-mg dose}}$ = TOC Clinical Cure Rate $_{\text{Placebo}}$
H_1: TOC Clinical Cure Rate $_{\text{Oral ibrexafungerp 300-mg dose}}$ ≠ TOC Clinical Cure Rate $_{\text{Placebo}}$

The p-value, odds ratio and 95% confidence interval will be presented in the ibrexafungerp 300-mg treatment arm compared to the placebo arm. Missing data for clinical outcome will be imputed using the NRI method described in Section 4.4. Additional summarizations will be performed by Candida Species of the baseline yeast, and the same inferential analysis will be performed, as appropriate.

The same inferential analysis employing the same methods as for the primary analysis will be performed for the ITT set and PP set to assess clinical cure at TOC visit. Missing data for clinical outcome will be imputed using the NRI method described in Section 4.4. No adjustment of type I error will be performed as these analyses are considered supportive to the primary analysis.

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.

Two subgroup analyses will be performed depending on Body Mass Index category (≤35 kg/m² or >35 kg/m²).

Analysis of time to resolution of signs and symptoms after initiation of study drug will use Kaplan-Meier method to estimate the median resolution time and its 2-sided 95% confidence intervals (CIs) based on the ITT, mITT, and PP sets. The time to resolution of signs and symptoms after initiation of study drug is defined as time (days) from first dose of study medication to the first resolution of signs and symptoms. Subjects who discontinued early will be censored at the last available assessment.

Kaplan-Meier curves for time to resolution of signs and symptoms after initiation of study drug will be provided by treatment group based on the ITT, mITT, and PP sets.

Summary of the number and percentage of subjects with continued clinical response at the Follow-up (FU) visit, which defined as continued absence of signs and symptoms in subjects who achieved Clinical Cure at the TOC visit, will be provided by treatment based on the ITT, mITT, and PP sets.

8.2. Secondary Efficacy Endpoints

8.2.1. Mycological outcomes

The percentage of subjects with mycological eradication (negative culture for growth of Candida species) at the TOC visit will be analyzed by Candida Species of the baseline yeast and overall, 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 TOC visit data for the mycological outcome will be imputed as mycological persistence using the NRI method described in Section 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;
- 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.

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

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.

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 and PP sets.

In addition, a summary table will be presented to include CLSI MIC range, mode, MIC50, and MIC90, based on the ITT and mITT sets by treatment group for the following MIC results:

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

8.2.2. Overall Outcome

The percentage of subjects with clinical cure and mycological eradication (overall outcome) at the TOC visit will be analyzed by Candida Species of the baseline yeast and overall, using the same inferential analysis employing the same methods as for the primary analysis as noted in Section 8.1.1. 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 clinical failure or mycological persistence.

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

8.2.3. Symptom Outcome

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

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

8.2.4. Clinical Improvement

The 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 analyzed using the same inferential analysis employing the same methods as for the primary analysis as noted in Section 8.1.1. 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 4.4. The composite score will be calculated as the rules described in Section 8.1.

In addition, a sensitivity analysis will be conducted based on the mITT set where the subjects with the imputed clinical improvement outcome using the NRI method at the TOC visit will be removed from the analysis.

8.2.5. Composite Score of the Vulvovaginal Signs and Symptoms

The following secondary efficacy endpoints will be analyzed using an analysis of covariance (ANCOVA) model having treatment group, site and diabetes mellitus diagnosis (Yes or No) as classification variables, and the baseline value as the continuous covariate.

- The change in signs and symptoms score from Baseline to TOC visit;
- The change in signs and symptoms score from Baseline to FU visit.

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.

A descriptive summary will be presented for the followings based on the mITT and PP sets:

- The change in total sign score from baseline to TOC and FU visits;
- The change in total symptom score from baseline to TOC and FU visits;
- The change in signs and symptoms score from TOC to FU visit.

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.

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 by treatment group.

Individual subject listings will be provided to support the tables.

9.1. Adverse Events

All AE summaries will be restricted to treatment-emergent AEs (TEAEs) only. A TEAE is defined as any event 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:

Missing 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.

Missing 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.

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.

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. 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 a 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.

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" has to 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 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 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 and clinically significant laboratory values will be identified.

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.

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 x the upper limit of normal (ULN);
- ALT or AST > 5 x ULN if new compared to Baseline;
- ALT or AST > 3 x ULN and total bilirubin >2 x ULN if new compared to Baseline;
- ALT or AST > 3 x ULN.

If subjects meet the criterion ALT or AST > 3 x ULN, the additional summary of the frequency and percentage of subjects with ALT or AST > 3 x ULN, confirmed by repeat test, and with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%) will be provided.

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 TOC visit will be presented. All vital sign data by subject will be presented in a listing.

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.

Any abnormalities noted during the physical examination will be presented in a listing for all subjects.

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 pH testing results will be summarized descriptively at the scheduled post-baseline visits by treatment group.

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 by-subject 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 secondary efficacy endpoint "Change from Baseline in Composite Score of the Vulvovaginal Signs and Symptoms" described in Section 8.2.5, an analysis of covariance (ANCOVA) model is 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, diabetes mellitus diagnosis (Yes or No), as justification factor in the efficacy analyses models.

12. References

Sobel, JD. Vaginal candidosis. Lancet 2007; 369:1961–71.

William G. Cochran (December 1954). "Some Methods for Strengthening the Common χ2 Tests". Biometrics. 10 (4): 417–451.

Gelman, Andrew (February 2005). "Analysis of variance? why it is more important than ever". The Annals of Statistics. 33 (1): 1–53.

13. Appendices

Appendix 1: Schedule of Assessments

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

Visit	V1 Screening[a]	V2 Baseline[a]	V3 TOC	V4 Follow-up	Unscheduled Visits
Day (allowable window)	**D-1 (-2)**	**D1**	**D11 (±3)**	**D25 (± 4)**	
Study Procedures					
Subject diary collection and review			X		
Vital Signs	X		X		If needed
Prior & concomitant medication review	X	X	X	X	X
AE monitoring	X	X	X	X	X

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

a. Screening and Baseline may occur on the same day.

b. For subjects under the legal age of consent, the subject's parent or legal representative will also sign the subject's ICF.

c. Results should be reviewed prior to randomization at Baseline (Day 1).

d. Hematology and blood chemistry. Safety laboratory tests will be performed by a qualified central laboratory.

e. If the subject experiences persistence or worsening or recurrence of symptoms, after the baseline visit, that per the investigator's assessment (e.g. symptoms ≥3) warrant the use of rescue antifungal therapy, the symptoms that led to the use of rescue antifungal therapy must be documented in the eCRF and a vaginal examination with rating of signs by the investigator should be completed. Additionally, vulvovaginal samples should be obtained for KOH testing and pH measurement (both at the site), fungal culture (central laboratory) and investigation of other pathogens such as bacterial vaginosis and *Trichomonas vaginalis* (at the site). If the investigator's rating of the vulvovaginal signs and vaginal samples collection are not possible prior to the initiation of the rescue therapy, they should still be completed as soon as possible after rescue therapy is initiated.

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

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

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