SCYNEXIS, Inc.

Clinical Trial Protocol

Oral Ibrexafungerp for the Treatment of Complicated Vulvovaginal Candidiasis (VVC) in Subjects who have failed Fluconazole Therapy

Protocol Number SCY-078-307b

NCT05399641

SCYNEXIS, Inc.

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Jersey City, NJ 07302

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Amendment 2: 17 January 2022 (Version 3.0)

1. CONTACT INFORMATION

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

2. PROTOCOL APPROVALS

PROTOCOL ID: SCY-078-307b

Oral Ibrexafungerp for the Treatment of Complicated Vulvovaginal Candidiasis (VVC) in Subjects who have failed Fluconazole Therapy

SCYNEXIS, Inc. Approval:

_____ _____

Date

3. INVESTIGATOR AGREEMENT STATEMENT

PROTOCOL ID: SCY-078-307b

Oral Ibrexafungerp for the Treatment of Complicated Vulvovaginal Candidiasis (VVC) in Subjects who have failed Fluconazole Therapy

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

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

_____ _____

Principal Investigator's Signature **Date**

_____

Principal Investigator's Name

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4. ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BID	Twice daily
CI	Confidence interval(s)
CPK	Creatinine phosphokinase
DDI	Drug-drug interaction
ECI	Event of clinical interest
EOT	End of treatment
eCRF	Electronic case report form
GCP	Good clinical practices
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GSI	Glucan synthesis inhibitors
Hct	Hematocrit
HgB	Hemoglobin
HIV	Human immunodeficiency virus
IB	Investigator's brochure
ICF	Informed consent form
ICH	International conference on harmonization
IRB/EC	Institutional review board/Ethics committee
ITT	Intent-to-Treat
IV	Intravenous
KOH	Potassium hydroxide
MedDRA	Medical dictionary for regulatory activities
MITT	Modified Intent-to-Treat

ABBREVIATION	DEFINITION
mg	Milligram
mL	Milliliter
OATP1B1 and OATP1B3	Transporters that are expressed on the sinusoidal membrane of hepatocytes; they accept a number of therapeutic reagents as their substrates. In vitro and in vivo studies have shown that some drugs inhibit these transporters and cause clinically relevant drug-drug interactions (DDIs).
QOL	Quality of Life
PI	Principal Investigator
PP	Per-Protocol
RBC	Red blood cell
RVVC	Recurrent Vulvovaginal Candidiasis
SAE	Serious adverse event
SAP	Statistical analysis plan
TEAE	Treatment emergent adverse event
WBC	White blood cell
VSS	Vulvovaginal Signs and Symptoms
VVC	Vulvovaginal candidiasis

5. PROTOCOL SYNOPSIS

TITLE: Oral Ibrexafungerp for the Treatment of Complicated Vulvovaginal Candidiasis (VVC) in Subjects who have failed Fluconazole Therapy

STUDY OBJECTIVES:

Primary Objective:

- To evaluate the efficacy of oral ibrexafungerp in subjects with complicated VVC who failed fluconazole therapy, based on clinical cure.

Secondary Objectives:

- To evaluate the efficacy of oral ibrexafungerp in subjects with complicated VVC who failed fluconazole therapy, based on mycological and clinical outcomes.
- To evaluate the safety and tolerability of oral ibrexafungerp in subjects with complicated VVC who failed fluconazole therapy.

Exploratory Objective

- To evaluate the efficacy of oral ibrexafungerp in subjects with complicated VVC who failed fluconazole therapy, based on Quality of Life (QOL) outcomes.

STUDY ENDPOINTS:

Primary Endpoint:

- Efficacy as measured by the percentage of subjects with clinical cure (total composite score of 0 on the Vulvovaginal Signs and Symptoms [VSS] Scale with no additional antifungal therapy required based on investigator's judgment) at the Test-of-Cure (TOC) visit

Secondary Endpoints:

Efficacy as measured by:

- The percentage of subjects with clinical improvement
  - Total composite score of 2 on the VSS Scale at the TOC and Follow-up (FU) visits.
  - Total composite score of 1 on the VSS Scale at the TOC and FU visits.
- The percentage of subjects with clinical success (at least 50% reduction from baseline in the total composite VSS score) at the TOC and FU visits.
- The percentage of subjects with mycological response (defined as a negative culture for growth of *Candida* spp. or subject is asymptomatic therefore culture not done) at the TOC and FU visits.
- The percentage of subjects with both clinical cure and mycological response at the TOC and FU visits.
- The percentage of subjects with clinical cure at the FU visits.
- The absolute change in total composite VSS score from baseline to the TOC and FU visits.

Exploratory Endpoints:

- Absolute improvement in QOL outcomes at TOC and FU visits compared to baseline as measured by QOL survey.
- Subjects whose signs and symptoms have resolved enough that additional antifungal treatment was not required based on clinical judgement.
- Time to resolution of symptoms.

Safety and tolerability as measured by:

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

STUDY PHASE: 3b

STUDY DESIGN:

This study is a Phase 3b, open-label, multicenter study to evaluate the efficacy and safety of oral ibrexafungerp in the treatment of subjects with complicated VVC episodes in subjects:

- not responsive to, **or**
- have isolates anticipated not to respond to, **or**
- who are refractory to or intolerant of fluconazole.

The susceptibility of historical isolates will be collected if available.

Approximately 150 eligible subjects will be enrolled. Subjects will be randomized to receive oral ibrexafungerp 300 mg administered twice a day (BID) for either one, three, or seven consecutive days, stratified by group based on *Candida* species and presence or absence of underlying medical conditions.

STUDY VISITS:

The study will consist of a Screening visit on Day -2 (±1), Baseline visit on Day 1 (if applicable, the Screening and Baseline visits can both be done on Day 1), Phone contacts on Days 3, 5 and 7 (±1), a TOC visit 14 (±3) days after Baseline, FU visits at: 14 days (±3) days after End Of Treatment (EOT), 30 (±4) after Baseline, 30 (±4) days after EOT and 60 (±4) days after EOT.

Screening (Day -2 (±1)**):** At Screening, subjects who are experiencing vulvovaginal symptoms will be evaluated by the investigator, who will obtain a vaginal sample for potassium hydroxide (KOH) testing and vaginal pH determination by the local laboratory. The vaginal samples will also be evaluated locally for findings indicative of bacterial vaginosis and Trichomonas vaginalis (WET Mount and/or DNA Probe). A vaginal sample for fungal culture and for species identification and susceptibility testing will be obtained and sent to a designated central laboratory. If the investigator suspects *Herpes* virus, *Neisseria gonorrhoeae,* or *Chlamydia trachomatis* infection, a vaginal sample will be collected and sent to the local laboratory. The investigators and the subjects will rate the signs and symptoms of infection, respectively, on the VSS Scale (see Appendix 2). Safety procedures, including an abbreviated physical exam, vaginal exam, vital signs, laboratory tests, and a pregnancy test will also be performed.

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

Baseline visit (Day 1): Subjects who meet all criteria for this study will complete a QOL questionnaire. They will receive the first dose of study drug, oral ibrexafungerp 300 mg, at the study site and will self-administer subsequent doses as applicable, at home. For some subjects, 300mg BID dosing will be

repeated daily for a total of 3 consecutive days (Days 1-3) or for 7 consecutive days (Days 1-7) based on *Candida* species and presence or absence of underlying medical conditions.

Phone Contact (Days 3, 5 and 7 [±1]): During this phone contact, AEs, resolution of symptoms, and concomitant medications (including antifungals) will be assessed.

TOC visit (14 days [±3] after Baseline): At this visit, treatment compliance will be reviewed and any AEs and/or concomitant medications evaluated. The investigators and the subjects will again rate the signs and symptoms of infection on the VSS Scale and the subjects will complete a QOL questionnaire

Vulvovaginal samples for fungal culture, species identification, and antifungal susceptibility testing will be obtained and sent to a designated central laboratory. Additional vaginal samples will be obtained for a KOH testing and vaginal pH by the local laboratory if symptoms persist or have worsened.

FU visit (14 days [±3] after EOT): At this visit, treatment compliance will be reviewed and any AEs and/or concomitant medications evaluated. The investigators and the subjects will again rate the signs and symptoms of infection on the VSS Scale and the subjects will complete a QOL questionnaire

Vulvovaginal samples for fungal culture, species identification, and antifungal susceptibility testing will be obtained and sent to a designated central laboratory. Additional vaginal samples will be obtained for a KOH test and vaginal pH measurement by the local laboratory if symptoms persist or have worsened.

FU visits 30 (±4) days after Baseline, 30 (±4) days after EOT and 60 (±4) days after EOT: At the FU visits, subjects will rate their symptoms of infection on the VSS Scale and will complete a QOL questionnaire. Only if VSS symptoms are present will the investigator perform a vulvovaginal examination to rate the subject's signs of infection, and collect samples for pH determination, KOH testing, and fungal culture.

A second treatment cycle (Cycle 2) will be allowed for subjects who did not achieve sufficient clinical improvement (e.g. VSS remains ≥3) on the randomized treatment (Cycle 1) as evaluated at the TOC visit or at the FU EOT+14 visits. The same visit schedule will be followed, starting with the Baseline visit.

TARGET POPULATION: The study population will include female subjects who are ≥18 years of age with complicated VVC who have failed fluconazole therapy.

KEY INCLUSION CRITERIA:

Subjects must fulfill all the following **KEY** criteria at Screening (Day -2 (±1)) to be eligible for study admission:

1) Subject is a post menarchal female ≥18 years of age at the time of signing the informed consent form (ICF).
2) Subject has a diagnosis of symptomatic VVC that meets the following criteria at the Screening visit:
   a) Minimum composite vulvovaginal signs and symptoms score of ≥4 with at least 2 signs or symptoms having a score of 2 (moderate) or greater on the VVS scale at baseline.
   b) Positive microscopic examination with 10% KOH in a vaginal sample collected at Screening revealing yeast forms (hyphae/pseudohyphae) or budding yeasts.
   c) Normal vaginal pH (≤ 4.5).
   d) Has no other vaginal co-infections based on WET Mount microscopic examination and/or DNA probe.
3) Subject should also have:

a) A VVC episode with persistence of symptoms despite fluconazole therapy (last dose of fluconazole must have been administered at least 7 days prior, but no longer than 28 days prior to screening).

OR

b) A recurrent vulvovaginal candidiasis (RVVC) episode with breakthrough symptoms while receiving maintenance antifungal therapy.

OR

c) A VVC episode caused by a non-*albicans candida species* known to have either intrinsic resistance to fluconazole e.g. *C.krusei* or suspected resistance to fluconazole, e.g. *C.glabrata, C auris* but likely without MIC data in hand.

OR

d) A VVC episode caused by a *candida* species with documented resistance to fluconazole based on MIC determination.

OR

e) A known history of azole allergy or intolerance.

4) Subject is able to take oral tablets.

KEY EXCLUSION CRITERIA:

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

1) Subject has any vaginal condition other than VVC that may interfere with the diagnosis or evaluation of response to therapy, such as concurrent causes of vulvovaginitis and/or cervicitis including bacterial vaginosis, *Trichomonas*, *Herpes* virus, *Neisseria gonorrhoeae*, *Chlamydia*, symptomatic human papillomavirus infection, or other mixed infections.
2) Subject received systemic and/or topical vaginal antifungal treatment, including prescription or over-the-counter products, within 7 days prior to the Screening visit. **Note: The screening visit may be rescheduled if required.**
3) Subject is receiving or anticipates requiring treatment with the prohibited medications within the specified timeframes per Appendix I.
4) Subject has active menstruation at the Screening visit. **Note: The Screening visit may be rescheduled if required.**
5) Subject has a history of or an active cervical/vaginal cancer.

STUDY DRUGS:

The study drug will be provided by SCYNEXIS Inc. as oral ibrexafungerp 150-mg tablets.

Treatment Cycle 1: ALL randomized subjects:

All subjects will receive open-label, oral ibrexafungerp 300mg BID (total daily dose of 600mg), for either one, three or seven consecutive days per the table below.

Ibrexafungerp Treatment Groups:

Treatment Group	Criteria	*Ibrexafungerp Dose (300mg AM and 300mg PM) Randomization and Stratification
Group A	Subjects without underlying medical conditions AND known to have isolates other than *C glabrata, C krusei, C auris*	1 Day dosing N=50
Group B	Subjects with underlying medical conditions: DM, immunocompromised conditions (e.g. HIV), debilitation, immunosuppressive therapy (e.g. corticosteroids), recurrent VVC (≥3 episodes/year) AND/ OR known to have *C glabrata, C krusei or C auris isolates*	3 Day OR 7 Days dosing Randomized 1:1 N=50:50

*Days of treatment is per CDC Guidelines (https://www.cdc.gov/std/treatment-guidelines/candidiasis.htm)

Enrollment will continue until the target number in each cohort is reached.

Treatment Cycle 2: A second treatment cycle will be allowed for subjects who did not achieve sufficient clinical improvement (e.g. VSS remains ≥3) on the randomized treatment (Cycle 1) as evaluated at the TOC visit or at the FU EOT+14 visits A second treatment cycle will also be allowed for subjects with clinical cure/improvement/success who experience a recurrence before the last FU visit. During Cycle 2, subjects may receive additional treatment with ibrexafungerp for a period up to 14 days as recommended by the investigator and following discussion with the sponsor.

It is recommended that study drug be administered with or immediately after a meal or snack.

STUDY BLINDING, RANDOMIZATION, AND STRATIFICATION: This is an open-label study. Subjects will be randomized to treatment, stratified by group based on the *Candida* species and presence or absence of underlying medical conditions.

STUDY EVALUATIONS

Efficacy Evaluations

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

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

Safety and Tolerability Assessments

Safety Evaluations: Safety will be evaluated throughout the study, from consent through the TOC visit, including the following parameters: AEs, concomitant medications, vital signs, safety laboratory tests, and study treatment discontinuations.

STATISTICAL ANALYSES:

All statistical tests will be two-sided and interpreted at a 5% significance level. The study is not powered for formal statistical comparisons. Descriptive statistics (i.e., mean, standard deviation, median, minimum, maximum, etc.) will be provided for all continuous variables; frequencies and percentages will be tabulated for incidence and categorical variables. For parameters measured over time, observed values and changes from baseline will be described for each time point. All analyses will be presented by treatment group. Unless otherwise stated, data will be analyzed as is with no imputation. No adjustment for multiplicity will be employed.

The primary efficacy endpoint, the percentage of subjects with clinical cure at TOC will be assessed on the MITT population and will present the clinical cure rate and the 95% confidence interval calculated using the method of Clopper and Pearson. In addition, the clinical cure rate and 95% CI will be calculated where subjects with missing values will be removed from the analysis.

Sample Size Determination

This is an exploratory study and no formal sample size calculation was performed. Approximately 150 subjects will be enrolled in allocation 50:50:50 in respect of 1, 3 and 7 days of treatment. Subjects will be randomized to treatment, stratified by group based on the *Candida* species and presence or absence of underlying conditions. The sample size of 150 is estimated to be adequate to perform an initial assessment of efficacy.

Analysis Populations

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

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

Modified Intent-to-Treat (MITT) Population: All treated subjects who have a positive culture for *Candida species* at Screening.

Per-Protocol (PP) Population: All MITT subjects who have completed the study drug treatment, who did not have major protocol deviations likely to affect study efficacy AND who have available data at the TOC evaluation.

Safety Population: All enrolled subjects who received at least one dose of study drug.

Efficacy Analysis

Efficacy assessments will be based on clinical evaluations, QOL outcomes, mycological testing, and additional antifungal use at the TOC visit. Analysis by species will be conducted.

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

Clinical Outcomes:

Clinical Cure: complete resolution of signs and symptoms with total composite score of 0 on the VSS Scale and with no additional antifungal therapy required based on investigator's judgment.

Clinical Improvement: partial resolution of signs and symptoms with total composite score of 1 or 2 on the VSS Scale and with no additional antifungal therapy required based on investigator's judgement.

Clinical Success: at least 50% reduction from Baseline in the total composite VSS score with no additional antifungal therapy required based on investigator's judgment.

Clinical Failure: Persistence and/or worsening of signs and symptoms or need for additional antifungal therapy.

Mycological Outcomes

Mycological Eradication: negative culture for growth of *Candida species*

Presumed Eradication: Subject is asymptomatic, therefore cultures not done

Mycological Persistence: positive culture for growth of *Candida* species

Safety Analysis

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

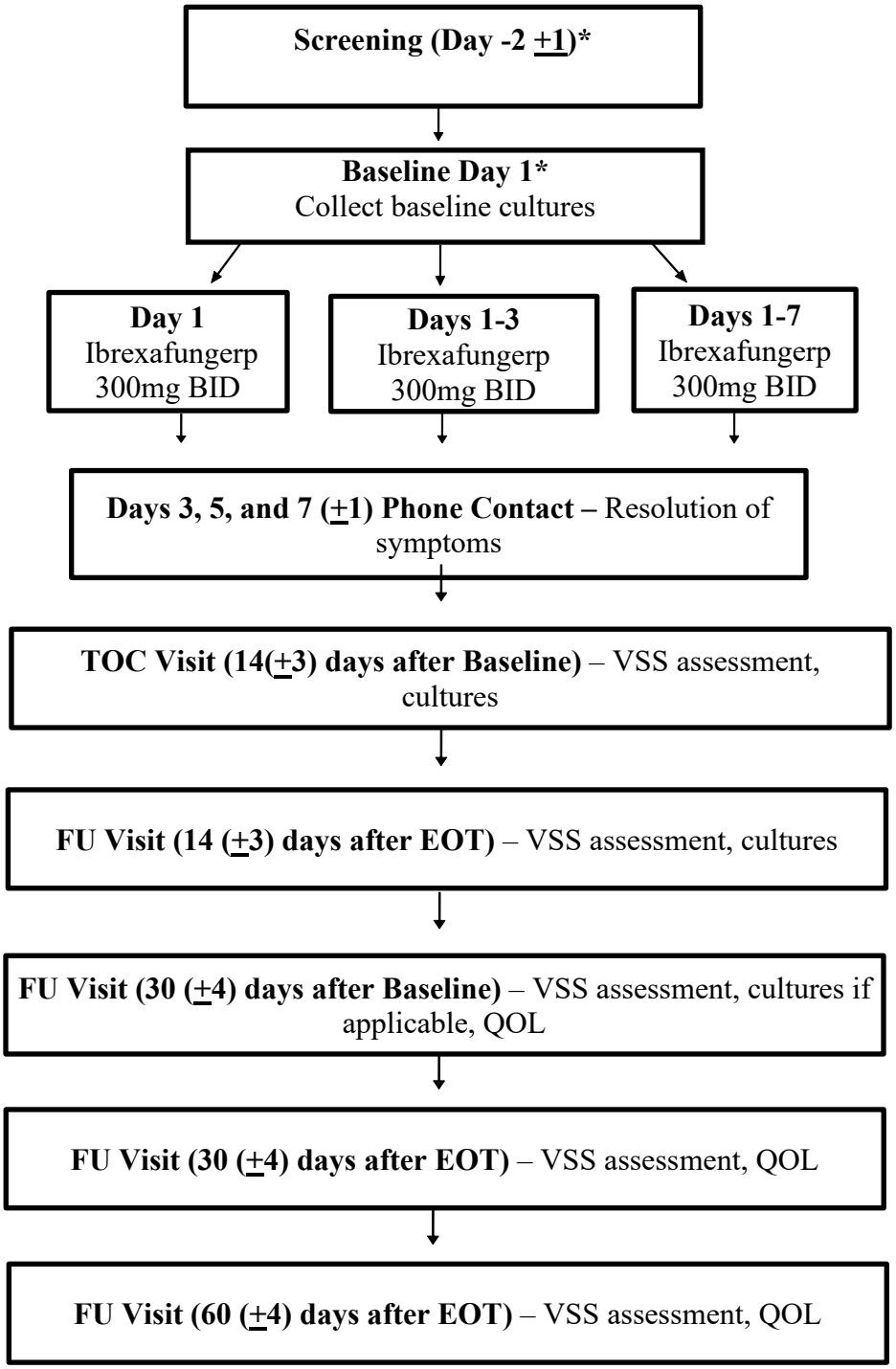
No formal statistical analysis is planned for the safety data. Safety analysis will be conducted using the Safety Population.

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

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

6. SCHEMATIC OF STUDY DESIGN

Figure 1: Schematic of Study Design



***Screening visit** can be done on the same day as Baseline visit if needed.

7. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

7.1. Background Information

Ibrexafungerp has been approved by the FDA for treatment of post menarcheal women with VVC.

7.1.1. Vulvovaginal Candidiasis

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

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

Current treatments for VVC include topical antifungals and the use of prescription oral antifungals such as single doses of fluconazole. In two vaginal candidiasis studies conducted with fluconazole, the therapeutic cure rate, defined as the resolution of signs and symptoms of vaginal candidiasis along with negative KOH examination and negative culture for *Candida,* was achieved by 55% of subjects receiving single doses of fluconazole 150 mg. The therapeutic cure rate is reduced to 40% in subjects with a history of recurrent vaginitis[4,5]. Although a single dose of fluconazole is able to provide an acceptable therapeutic outcome for more than half of the treated individuals, the emergence of fluconazole resistance among *C. albicans* isolates and the frequency of cases caused by *C. glabrata,* a strain naturally less susceptible to fluconazole, signals the need for new therapeutic approaches.

Additionally, recurrence of VVC after fluconazole therapy is not uncommon and these exacerbations often involve the same microorganism identified in the initial episode, suggesting that a small number of *C. albicans* remain as a reservoir in the vagina after completion of azole therapy, becoming the source of subsequent exacerbations[6]. This may be explained by the fact that azoles are fungistatic, which means that they slow the growth of, but do not kill, the fungus and azoles are not active against certain species of *Candida* that cause VVC.

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

This study aims to provide evidence of the efficacy and evaluate the safety of oral ibrexafungerp as a new class of antifungal agent with fungicidal activity against *Candida* spp. in the treatment of complicated VVC in subjects who have failed fluconazole therapy.

7.1.2. The glucan synthesis inhibitor ibrexafungerp (formerly known as SCY-078)

Ibrexafungerp is a member of a new class of antifungal agents and is an orally active, semi-synthetic, triterpenoid derivative of the natural product enfumafungin. Ibrexafungerp is a

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

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

7.1.3. Antifungal activity

The spectrum and potency of activity of ibrexafungerp has been evaluated by numerous independent laboratories against an extensive panel of clinically relevant yeast and mold isolates using the Clinical and Laboratory Standards Institute (M27-A3 guidelines)[7] and European Committee on Antimicrobial Susceptibility Testing methods. Overall, the epidemiological studies have demonstrated that ibrexafungerp has potent, broad-spectrum activity against the majority of the clinical isolates tested. These studies have laid the foundation in support of the use of ibrexafungerp for the treatment of invasive fungal infections[8,9,10].

7.1.3.1. Activity against *Candida* spp.

Ibrexafungerp has been evaluated against >2000 *Candida* isolates, including all clinically relevant species with more than 300 *C. albicans, more than* 600 *C. glabrata* and more than 250 *C. auris* isolates tested. These *in vitro* studies have demonstrated the broad spectrum of anti-*Candida* activity of ibrexafungerp. Additionally, ibrexafungerp demonstrated *in vitro* activity against pre-formed biofilms, which is a relevant feature when addressing catheter-related *Candida* infections and, potentially, VVC. Studies conducted with azole- and echinocandin- resistant strains have shown that ibrexafungerp retains activity (i.e., no significant change in minimum inhibitory concentration [MIC] compared to wild type) against >90% of azole- resistant strains and >70% of *Candida* strains with *FKS* mutations commonly associated with echinocandin resistance. Interestingly, although ibrexafungerp and the echinocandins share a similar mechanism of action (β-[1,3]-D-glucan synthesis inhibition), their clearly different molecular structure provides them with some differentiating characteristics in terms of microbiological activity.

Ibrexafungerp was evaluated *in vitro* against approximately 190 clinical isolates of echinocandin-resistant strains of *Candida* spp. containing mutations in the *FKS* gene. Overall, ibrexafungerp was active against the majority of the echinocandin-resistant strains tested. Moreover, ibrexafungerp was significantly active against approximately 70% of the isolates containing the most commonly reported *FKS* mutation associated with echinocandin resistance in *C. glabrata* (S663P in *FKS2* and S645P in *FKS1*). Selection of ibrexafungerp resistance *in vitro* occurs at a low frequency. A deletion at position F659 in *FKS2* of *C. glabrata* was the predominant mutation observed in these studies; notably, ibrexafungerp did not select for mutations at positions S663 or S645. These results suggest that ibrexafungerp inhibits glucan synthase in a manner different to echinocandins.

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

over 100 different *C. auris* isolates, at concentrations indicative of potential clinically relevant effects. *C. auris* has been recently highlighted as a clinical alert by the Centers for Disease Control and Prevention (CDC) because of the global emergence of this fungal infection with limited therapeutic options and high mortality.

7.1.4. Clinical experience

To date, more than 1500 healthy subjects and patients have been exposed to ibrexafungerp in completed and ongoing clinical trials.

Ibrexafungerp was generally well tolerated following single oral doses of up to 1600 mg and multiple oral doses of up to 800 mg/day for 28 consecutive days in Phase 1 studies. Reported adverse events (AEs) after oral administration have been generally transient and primarily mild to moderate in intensity. The most frequently reported AEs have been mild gastrointestinal (GI) events (nausea, vomiting, diarrhea and abdominal pain).

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

The primary objective of this study was to evaluate the efficacy of oral ibrexafungerp in female subjects 12 years and older with VVC by comparing the clinical outcomes of ibrexafungerp and placebo. The primary end point of the study was efficacy as measured by the percentage of subjects with clinical cure (complete resolution of signs and symptoms) at the test-of-cure (TOC) visit.

Approximately 366 eligible subjects were enrolled and randomly assigned in a 2:1 ratio to receive ibrexafungerp (300-mg dose twice daily [BID]) or matching placebo administered BID for 1 day.

Overall, the percentage of subjects with clinical cure at the TOC visit was statistically significantly higher for the ibrexafungerp group than the placebo group (50.5% versus 28.6%; P=0.001).

Ibrexafungerp was generally well-tolerated by subjects with AVVC when administered as a 300-mg oral dose (two 150mg tablets) BID for 1 day. Overall, a total of 150 subjects (60.7%) of the 247 subjects who received ibrexafungerp and 63 subjects (50.8%) of the 124 subjects who received placebo experienced at least 1 TEAE during the study.

The most frequently reported adverse events were gastrointestinal disorders, which were reported at a higher frequency for the ibrexafungerp group than the placebo group. The most frequently reported GI disorders in the ibrexafungerp groups included diarrhea and nausea (in more than 10% of subjects).

Three (3) subjects reported SAEs during the study: 2 SAEs were reported by 1 subject (0.4%) who received ibrexafungerp (pneumonia and bronchial hyperreactivity), and 2 SAEs were reported by 2 subjects (1.6%) who received placebo (diabetes mellitus and hypokalemia); none were considered to be related to the study drug.

A total of 5 subjects in the ibrexafungerp group experienced TEAEs that resulted in discontinuation. Of these, 2 subjects experienced TEAEs leading to withdrawal of the study drug and discontinuation from the study (vomiting and dizziness). In addition, 3 subjects experienced

TEAEs leading to discontinuation after completing study treatment (bacterial vaginosis and vulvovaginal itching; not related to study drug). There were no deaths reported during the study.

Mean clinical laboratory results and vital sign measurements observed at the TOC visit were generally similar to those observed at baseline, with no notable differences between treatment groups.

SCY-078-306, *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*

A total of 455 subjects were enrolled, and 449 subjects received at least 1 dose of randomized study drug, 298 subjects received ibrexafungerp and 151 subjects received placebo.

The primary objective was to evaluate the efficacy of oral ibrexafungerp versus placebo in female subjects 12 years and older with VVC by comparing the clinical outcomes of ibrexafungerp and placebo. Efficacy was defined as the percentage of subjects with clinical cure (complete resolution of signs and symptoms) at the TOC visit. The primary analysis was conducted using the Modified Intent-to-Treat (mITT) set, which included 272 randomized subjects (188 subjects in the ibrexafungerp group and 84 subjects in the placebo group) who had a diagnosis of symptomatic AVVC and a positive culture for *Candida* species at baseline. The study achieved the primary endpoint reaching statistical significance. Overall, the percentage of subjects with clinical cure at the TOC visit in the mITT set was statistically significantly higher for the ibrexafungerp group than the placebo group (63.3% versus 44.0%; P=0.007).

Ibrexafungerp was generally well-tolerated by subjects with AVVC when administered as a 300-mg oral tablet BID for 1 day.

Overall, a total of 99 subjects (33.2%) of the 298 subjects who received ibrexafungerp and 44 subjects (29.1%) of the 151 subjects who received placebo experienced at least 1 TEAE during the study.

The most frequently reported adverse events were GI disorders. The percentage of subjects who experienced treatment-related TEAEs was higher for the ibrexafungerp group than the placebo group (14.8% versus 4.0%, respectively), however the majority of these were GI disorders and were considered mild in severity.

A total of 2 subjects reported SAEs during the study: 1 subject from the ibrexafungerp group reported a gastrointestinal bacterial infection and 1 subject from the placebo group reported diabetic ketoacidosis.

Three subjects experienced a TEAE leading to study discontinuation, all in the ibrexafungerp group (diabetes mellitus [1 subject] and bacterial vaginosis [2 subjects]).

Mean clinical laboratory results and vital sign measurements observed at the TOC visit were generally similar to those observed at baseline, with no notable differences between treatment groups.

For additional information on ibrexafungerp, please refer to the Investigator´s Brochure (IB).

7.2. Rationale for the Study

This study is an exploratory, open-label study to evaluate the efficacy and safety of oral ibrexafungerp for the treatment of complicated VVC in subjects who have failed fluconazole therapy. The study design follows the CDC, ACOG and IDSA guidelines on the treatment of patients with complicated VVC.

7.2.1. Rationale for Study Indication and Population

Considering the properties of ibrexafungerp as a potent antifungal compound, with fungicidal activity against *Candida* spp., it will represent an important non-azole alternative treatment for subjects suffering from VVC who are not responsive to fluconazole. The Phase 3 VANISH program for treatment of VVC with ibrexafungerp excluded patients with treatment failure and patients who had immunocompromised underlying medical conditions that complicated VVC.

These women with VVC infections excluded from the VANISH study are the intended population for this study that is designed to facilitate the identification of a clinically meaningful effect of ibrexafungerp.

7.2.2. Rationale for Selected Dose Levels and Dosing Regimens

The selected oral ibrexafungerp dose regimen for this study will be BID doses of 300 mg, given for 1, or for 3 or 7 consecutive days. Oral ibrexafungerp 300 mg BID is the current approved dose for VVC. The current CDC, ACOG and IDSA guidelines recommend 3-7 days of treatment for complicated VVC and 7-14 days of treatment for non-*albicans* VVC. These dose regimens are in the range of doses that have been well tolerated in Phase 1, Phase 2, and ongoing Phase 3 studies.

7.2.3. Rationale for Study Endpoints

Study endpoints were selected in line with prior efficacy and safety studies in patients with VVC episodes.

7.2.4. Rationale for Study Design

This trial is being conducted as a phase 3b, open-label, ibrexafungerp only treatment for VVC. The duration of treatment and the subsequent evaluations and endpoints are consistent with prior clinical trials in patients with VVC

8. STUDY OBJECTIVES

8.1. Primary Objectives

- To evaluate the efficacy of oral ibrexafungerp in subjects with complicated VVC who failed fluconazole therapy, based on clinical cure.

8.2. Secondary Objectives

- To evaluate the efficacy of oral ibrexafungerp in subjects with complicated VVC who failed fluconazole therapy, based on mycological and clinical outcomes.

- To evaluate the safety and tolerability of oral ibrexafungerp in subjects with complicated VVC who failed fluconazole therapy.

8.3. Exploratory Objective

- To evaluate the efficacy of oral ibrexafungerp in subjects with complicated VVC who failed fluconazole therapy, based on QOL outcomes.

9. STUDY ENDPOINTS

9.1. Primary Endpoints

- Efficacy as measured by the percentage of subjects with clinical cure (total composite score of 0 on the VSS Scale with no additional antifungal therapy required based on investigator's judgment) at the TOC visit.

9.2. Secondary Endpoints

Efficacy as measured by:

- The percentage of subjects with clinical improvement:
  - Total composite score of 2 on the VSS scale at the TOC and FU visits
  - Total composite score of 1 on the VSS scale at the TOC and FU visits
- 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 and FU visits.
- The percentage of subjects with mycological response (defined as a negative culture for growth of *Candida* spp. or subject is asymptomatic, therefore culture not done) at the TOC and FU visits.
- The percentage of subjects with both clinical cure and mycological response at the TOC and FU visits.
- The percentage of subjects with clinical cure at the FU visits.
- The absolute change in total composite VSS score from baseline to the TOC and FU visits.

Exploratory Endpoints:

- Absolute improvement in QOL outcomes at TOC and FU visits compared to baseline as measured by QOL survey.
- Subjects whose signs and symptoms have resolved enough that additional antifungal treatment was not required based on clinical judgement.
- Time to resolution of symptoms.

Safety and tolerability as measured by:

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

10. STUDY DESIGN

10.1. Overall Description of the Study

This study is Phase 3b, open-label, multicenter study to evaluate the efficacy and safety of oral ibrexafungerp in the treatment of subjects with VVC episodes in subjects:

- not responsive to, **or**
- have isolates anticipated not to respond to, **or**
- who are refractory to or intolerant of fluconazole.

The susceptibility of historical isolates will be collected where available.

Approximately 150 eligible subjects will be enrolled. Subjects will be randomized to receive oral ibrexafungerp 300mg administered twice a day for either one, three, or seven consecutive days, stratified by group based on *Candida* species and presence or absence of underlying medical conditions.

10.1.1. Study Visits

The study will consist of a Screening visit on Day -2 (±1), Baseline visit on Day 1 (if applicable, the Screening and Baseline visits can both be done on Day 1), Phone contacts on Days 3, 5 and 7 (±1), a TOC visit 14 (±3) days after Baseline, FU visits at: 14 (±3) days after EOT, 30 (±4) after Baseline, 30 (±4) after EOT and 60 (±4) days after EOT.

10.1.1.1. Screening (Day -2)

At Screening, subjects who are experiencing vulvovaginal symptoms will be evaluated by the investigator, who will obtain a vaginal sample for potassium hydroxide (KOH) testing and vaginal pH determination by the local laboratory prior to randomization and initiation of treatment. The vaginal samples will also be evaluated locally for findings indicative of bacterial vaginosis and *Trichomonas vaginalis* (WET Mount and/or DNA probe). If the investigator suspects *Herpes* virus, *Neisseria gonorrhoeae or Chlamydia trachomatis* infection, a vaginal sample will be collected and sent to a qualified local laboratory. A vaginal sample for fungal culture and for species identification and susceptibility testing will be obtained and sent to a designated central laboratory. The investigators and the subjects will rate the signs and symptoms of infection, respectively, on the VSS Scale (see Appendix 2). Safety procedures, including an abbreviated physical exam, vaginal exam, vital signs, laboratory tests and a pregnancy test will also be performed.

To be eligible for inclusion, subjects must have a minimum composite score of vulvovaginal signs and symptoms ≥ 4 with at least 2 signs or symptoms having a score of 2 (moderate) or greater in the VSS Scale at Baseline, a positive KOH test, a normal vaginal pH (≤4.5) and confirmed absence of other vaginal co-infections.

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

10.1.1.2. Baseline (Day 1)

Subjects who meet all criteria for this study will complete a QOL questionnaire. They will receive the first dose of study drug, oral ibrexafungerp 300 mg, at the study site and will self-administer subsequent doses as applicable at home. For some subjects, 300mg BID dosing will be repeated daily for a total of 3 or 7 consecutive dosing days based on *Candida* species and presence or absence of underlying medical conditions. Doses will be self-administered at 12-hourly (±3 hours) intervals.

10.1.1.3. Phone Contact (Days 3, 5 and 7[±1])

During this phone contact, AEs, resolution of symptoms (applicable section of the VSS scale), and concomitant medications (including antifungals) will be assessed.

10.1.1.4. TOC visit (14 ±3 days after Baseline)

At this visit, study drug container(s) will be returned, reviewed, and treatment compliance evaluated. The investigators and the subjects will again rate the signs and symptoms of infection on the VSS Scale and the subjects will complete a QOL questionnaire.

Vulvovaginal samples for fungal culture, species identification, and antifungal susceptibility testing will be obtained and sent to a designated central laboratory. Additional vaginal samples will be obtained for a KOH test and pH measurements by the local laboratory if symptoms persist or have worsened. AEs and/or concomitant medications will be evaluated.

10.1.1.5. FU visit (14 ±3 days after EOT)

At this visit, study drug container(s) will be returned, reviewed, and treatment compliance evaluated. The investigators and the subjects will again rate the signs and symptoms of infection on the VSS Scale and the subjects will complete a QOL questionnaire.

Vulvovaginal samples for fungal culture, species identification, and antifungal susceptibility testing will be obtained and sent to a designated central laboratory. Additional vaginal samples will be obtained for a KOH and vaginal pH testing by the local laboratory if symptoms persist or have worsened. AEs and/or concomitant medications will be evaluated.

10.1.1.6. FU visits 30 (±4) days after Baseline, 30 (±4) days after EOT and 60 (±4) days after EOT:

At the FU visits, subjects will rate their symptoms of infection on the VSS Scale and will complete a QOL questionnaire. Only if VSS symptoms are present will the investigator perform a vulvovaginal examination to rate the subject's signs of infection and collect samples for pH determination, KOH testing, and fungal culture.

10.1.1.7. All Visits

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

10.1.2. Study Assessments

The study will include efficacy, safety, and tolerability assessments.

10.1.2.1. Efficacy Assessments

Efficacy assessments will be based on VSS scores, clinical evaluations, QOL outcomes, mycological testing and additional antifungal use assessed at the TOC and FU visits.

10.1.2.2. Safety Assessments

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

10.2. Blinding, Randomization, and Stratification

This is an open label study. Subjects will be randomized to treatment, stratified by group based on the *Candida* species and presence or absence of underlying medical conditions.

10.3. Study Duration

Each subject is expected to complete the study in approximately 65 days and up to approximately 130 days for subjects who require additional treatment and enter Treatment Cycle 2.

10.4. Number of Centers

Multiple centers will participate in subject enrollment and treatment.

11. STUDY POPULATION

The study population will include female subjects who are ≥18 years of age with complicated VVC who have failed fluconazole therapy.

11.1. Inclusion Criteria

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

1) Subject is a post menarchal female ≥18 years of age at the time of signing the ICF.
2) Subject has a diagnosis of symptomatic VVC that meets the following criteria at the Screening visit:
   a) Minimum composite vulvovaginal signs and symptoms score of ≥4 with at least 2 signs or symptoms having a score of 2 (moderate) or greater on the VSS scale at baseline.
   b) Positive microscopic examination with 10% KOH in a vaginal sample collected at Screening revealing yeast forms (hyphae/pseudohyphae) or budding yeasts
   c) Normal vaginal pH (≤ 4.5).
   d) Has no other vaginal co-infections based on WET Mount microscopic examination (and/or DNA probe).
3) Subject should also have:
   a) A VVC with persistent symptoms despite fluconazole therapy (last dose of fluconazole must have been administered at least 7 days prior, but no longer than 28 days prior to screening.

OR

b) A recurrent vulvovaginal candidiasis (RVVC) episode with breakthrough symptoms while receiving maintenance antifungal therapy.

OR

c) A VVC episode caused by a non-*albicans candida species* known to have either intrinsic resistance to fluconazole e.g. *C.krusei* or suspected resistance to fluconazole, e.g. *C.glabrata, C auris* but likely without MIC data in hand.

OR

d) A VVC episode caused by *candida* species with documented resistance to fluconazole based on MIC determination.

OR

e) A known history of azole allergy or intolerance.

4) Subject is able to take oral tablets.

5) Subject is not pregnant or lactating and plans not to become pregnant. Women of childbearing potential < 1 year post-menopausal must agree to and comply with using one barrier method (male condom, female condom, and diaphragm) plus one other highly effective method of birth control, or sexual abstinence, from the time of consent through 10 days after the completion of study therapy. **Subjects must refrain from using any topical vaginal contraceptives as these may have an impact on the signs and symptoms of VVC.**

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

6) Subject is able to understand and sign a written ICF, which must be obtained prior to treatment and any study-related procedures.

7) Subject is able to understand and sign a consent or authorization form, which shall permit the use, disclosure and transfer of the subject's personal health information (e.g., in the US Health Information Portability and Accountability Act Authorization form).

8) Subject is able to understand and follow all study-related procedures including study drug administration.

11.2. Exclusion Criteria

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

1) Subject has any vaginal condition other than VVC that may interfere with the diagnosis or evaluation of response to therapy, such as concurrent causes of vulvovaginitis and/or cervicitis including bacterial vaginosis, *Trichomonas*, *Herpes* virus, *Neisseria gonorrhoeae*, *Chlamydia*, symptomatic human papillomavirus infection, or other mixed infections.

2) Subject received systemic and/or topical vaginal antifungal treatment, including prescription or over-the-counter products, within 7 days prior to the Screening visit. **Note: The screening visit may be rescheduled if required.**
3) Subject is receiving or anticipates requiring treatment with the prohibited medications within the specified timeframes per Appendix I.
4) Subject has active menstruation at the Screening visit. Note: **The Screening visit may be rescheduled if required**.
5) Subject has a history of or an active cervical/vaginal cancer.
6) Subject has a known hypersensitivity to any of the components of the formulation.
7) Subject has participated in any other investigational study within at least 30 days (or 5.5 half-lives of the investigational product) before signing the ICF.
8) Subject has received prior treatment with ibrexafungerp.
9) Subject has any other condition or laboratory abnormality (such as severe hepatic impairment) that, in the judgment of the investigator, would put the subject at unacceptable risk for participation in the study or may interfere with the assessments included in the study.
10) Subject is unlikely to comply with protocol requirements.

11.3. Discontinuation Criteria

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

- Withdrawal of consent by the subject
- Investigator or sponsor decision that withdrawal is in the subject's best interest
- Occurrence of an AE that, in the opinion of the investigator, warrants discontinuation of the subject from the study drug
- Lost to follow up (every attempt should be made to contact the subject)

The reason for a subject's discontinuation of treatment or withdrawal from the study will be clearly documented in the source documents and on the electronic case report form (eCRF). All TOC procedures should be performed for subjects who discontinue from the study before the TOC visit.

11.4. Early Termination

If the subject experiences persistence or worsening or recurrence of symptoms that per the investigator's assessment (e.g., symptoms ≥4) warrant the use of additional antifungal therapy, and the investigator does not consider continuing treatment with ibrexafungerp for a Second Treatment Cycle, a vaginal examination with investigator's rating of signs should be completed. Additionally, vulvovaginal samples should be obtained for KOH testing and pH measurements by the local laboratory, fungal culture by the central laboratory and investigation of other pathogens such as bacterial vaginosis and *Trichomonas vaginalis* by the local laboratory.

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

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

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

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

11.5. Replacement of Dropouts

Subjects who discontinue from the study may be replaced at the discretion of the investigator and Sponsor.

12. STUDY TREATMENTS

12.1. Study Treatment Groups

Treatment Cycle 1 – ALL randomized subjects:

Subjects who meet all the inclusion and none of the exclusion criteria will be randomized to treatment and stratified by group based on the *Candida* species and presence or absence of underlying conditions. Subjects will receive open-label oral ibrexafungerp 300 mg BID for one, three or seven consecutive days per the table below:

Ibrexafungerp Treatment Groups:

Treatment Group	Criteria	*Ibrexafungerp Dose (300mg AM and 300mg PM) Randomization and Stratification
Group A	Subjects without underlying medical conditions AND known to have isolates other than *C glabrata, C krusei, C auris*	1 Day dosing N=50
Group B	Subjects with underlying medical conditions: DM, immunocompromised conditions (e.g. HIV), debilitation, immunosuppressive therapy (e.g. corticosteroids), recurrent VVC (≥3 episodes/year) AND/OR known to have *C glabrata, C krusei or C auris isolates*	3 Days OR 7 Days dosing Randomized 1:1 N=50:50

*Days of treatment is per CDC Guidelines (https://www.cdc.gov/std/treatment-guidelines/candidiasis.htm)

Enrollment will continue until the target number in each cohort is reached.

Treatment Cycle 2: A second treatment cycle will be allowed for subjects who did not achieve sufficient clinical improvement (e.g. VSS remains ≥3) on the randomized treatment (Cycle 1) as evaluated at the TOC and FU visits. A second treatment cycle will also be allowed for subjects with clinical cure/improvement/success who experience a recurrence before the last FU visit. During Cycle 2, subjects may receive additional treatment with ibrexafungerp for a period up to 14 days as recommended by the investigator and following discussion with the sponsor.

12.2. Dietary Requirements

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

12.3. Study Drugs

Study drug will consist of oral ibrexafungerp (150 mg tablets).

12.4. Ibrexafungerp Description

Study Drug Identifier: ibrexafungerp

12.4.1. Formulation, Packaging and Labelling

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

Oral tablets will be supplied in blister packs of four 150 mg tablets per blister. Each blister constitutes one day's dosing of 300 mg BID. Labels on the blisters will contain study medication information and any other information required by applicable regulations and may include the following information:

- Product Name
- Sponsor Name
- Study Protocol Number
- Place to write the subject number
- Number of tablets per blister pack
- Dosing instructions
- Storage conditions (e.g. room temperature 15°C – 25°C
- Caution Statement: e.g. "Caution: New Drug – Limited by Federal (United States) Law to Investigational Use Only"

12.4.2. Storage and Stability

The pharmacist or appropriate designee at each clinical research site will be responsible for the study drug. For long-term storage at the site, study drug supplies provided in blisters must be kept in a secure area (e.g., locked cabinet) and stored at room temperature.

12.5. Drug Accountability

The investigator or designee will inventory and acknowledge receipt of all shipments of the study drug. Drug accountability logs will be used to maintain accurate records of receipt, dispensing, administration to each subject and return of drug. A study monitor will periodically check the supplies of investigational products held by the site to verify accountability of all study drugs. At the conclusion of the study after final drug accountability has been completed by the monitor, all unused study drug and all empty/partially used blisters will be returned to the Sponsor or destroyed on site if the site has procedures in place for study drug destruction.

Drug supplies will be maintained in a secure, limited-access storage area under the recommended storage conditions (see Section 12.4.2).

The study drug supplied for this study is only for use in subjects properly consented and enrolled under this protocol. A study site designee (e.g. pharmacist, study nurse/coordinator) will:

- Record the treatment in the appropriate drug accountability log
- Report and document any study medication issues such as crushed or broken tablets
  - All product quality complaints should be reported to the Sponsor
- Collect blister packs (containers) and count the number of tablets remaining at the TOC visit.
- Record any unused or remaining drug in the drug accountability log and eCRF and note any discrepancies and reason for discrepancies

12.6. Subject Compliance with Study Drug Dosing

Subjects will be instructed to bring the assigned blister packs of study medication (including empty blister packs) with them to the TOC visit to assess treatment compliance. Compliance will be assessed based on remaining tablets as compared to what should have been taken. Details of treatment including any missing dose will be recorded on the eCRF. Sites are encouraged to contact the medical monitor or sponsor for concerns of compliance with the treatment regimen, especially for subjects who miss doses due to problems with tolerability.

13. NON-STUDY TREATMENTS

13.1. Prior and Concomitant Medications

All medications (including prescription and over-the-counter medications, supplements, and herbal products) taken from 30 days before the Screening Visit (Day -2 [± 1]) through the TOC

visit will be recorded in the eCRF. Only the use of antifungal medications, medications used to treat vaginal infections, vaginal (topical) medications, antibiotics for any reason or any other medications to treat a study-drug related AE will be recorded after the TOC visit through the last study visit (FU). Start and stop dates of concomitant medications will be recorded in the eCRF. Prior and concomitant medications will be reviewed and recorded at all scheduled and unscheduled study visits.

13.2. Prohibited Medications

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

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

See Section 21 (Appendix 1) for the full list of prohibited medications.

13.2.1. Medications to be Administered with Caution and Monitored as Appropriate

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

- CYP3A4 substrates, including but not limited to sirolimus, tacrolimus warfarin, cyclosporine and amiodarone
- Organic anion-transporting polypeptide 1B3 (OATP1B3) substrates

See Section 21 (Appendix 1) for the full list of medications to be administered with caution.

13.3. Study Restrictions

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

14. STUDY PROCEDURES

The following sections provide a description of the individual study procedures to be performed during the conduct of the study. Detailed schedules of study assessments are provided in the Schedule of Visits and Procedures in Table 1.

14.1. Informed Consent

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

14.2. Assignment of Subject Number

At Screening, all subjects who have signed an ICF will receive a unique subject identification (ID) number, which will consist of a site number followed by a 2-digit sequentially assigned subject number starting at 01, at each site. The subject numbers assigned to eligible subjects will be recorded in the eCRF. This number will be unique to each subject and will be used to identify the subject throughout the study.

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

14.3. Inclusion and Exclusion Criteria

All inclusion and exclusion criteria will be reviewed at Screening (-2 $\pm$1) and at Baseline (Day 1) to ensure that the subject qualifies for the trial. Screening and Baseline can be on the same day, if applicable.

14.4. Medical History and Demographics

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

14.5. Abbreviated Physical Examination

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

14.6. Urine Pregnancy Test

A urine pregnancy test based on the measurement of human chorionic gonadotropin with a sensitivity of at least 25 international units per liter will be performed at Screening and at unscheduled visits, if needed, by the local laboratory for all subjects of childbearing potential. The pregnancy test results will be reviewed at Baseline (Day 1) before administration of study drug.

14.7. Safety Laboratory Tests

Safety laboratory tests will be performed by a qualified local laboratory. Samples for safety laboratory tests will be collected at the Screening, TOC, and at any unscheduled visit, if needed. If indicated, these may be done more frequently as follow up to a laboratory abnormality.

The following laboratory parameters will be determined:

14.7.1. Hematology

- White blood cell (WBC) count
- Hemoglobin (HgB)

- Red blood cell (RBC) count
- Hematocrit (Hct)
- Platelet count
- Differential WBC count will include percentages for lymphocytes, monocytes, eosinophils and basophils,
- and absolute counts for neutrophils, lymphocytes, atypical lymphocytes, monocytes, eosinophils and basophils.

14.7.2. Blood Chemistry

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

14.8. Rating of Vulvovaginal Symptoms by the Subject Using the VSS Scale

Subjects will be asked to rate their vulvovaginal symptoms at Screening, Baseline (Day 1), during telephone interviews on Days 3, 5 and 7, at the TOC visit and at the FU visits.

Subjects will also assess their symptoms at unscheduled visits, as needed.

If the subject experiences persistence or worsening or recurrence of symptoms that per the investigator's assessment (e.g. symptoms ≥4) warrant the use of rescue antifungal therapy, the rating of the symptoms that led to the use of rescue antifungal therapy must be documented in the eCRF and a vaginal examination with rating of signs by the investigator should be completed. If the investigator's rating of the vulvovaginal signs and vaginal samples collection are not possible prior to the initiation of the rescue therapy, they should still be completed as soon as possible after rescue therapy is initiated.

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

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

14.9. Vulvovaginal Samples for Identification of Other Pathogens and Vaginal pH

A vulvovaginal specimen will be obtained at the Screening visit for local vaginal pH determination. This sample will also be tested by a local qualified laboratory to rule out bacterial vaginosis and *Trichomonas vaginalis.* Testing for *Neisseria gonorrhoeae*, *Chlamydia trachomatis* or *Herpes* virus will also be conducted by a qualified local laboratory if clinically indicated. Vaginal samples will be tested for bacterial vaginosis, *T. vaginalis, N. gonorrhoeae*, *C.*

trachomatis or *Herpes* virus at unscheduled visits, if needed. Samples should be collected prior to the initiation of rescue therapy, and if not possible, it should still be completed as soon as possible after rescue therapy is initiated. If there is persistence or recurrence of vulvovaginal symptoms, additional vulvovaginal specimens will be collected at the TOC and at the FU visits.

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

14.10. Vulvovaginal Samples for KOH and Fungal Culture

At Screening, a vulvovaginal specimen will be obtained for direct microscopic examination with 10% KOH. Subjects must have a positive KOH test at screening to be enrolled. The screening KOH will be assessed at the site by the investigator or qualified designee. A vaginal sample will also be obtained at screening, at the TOC and at the first FU visit at 14 days after EOT for fungal culture and species identification by the central laboratory and for susceptibility testing against ibrexafungerp and additional antifungal agents (per CLSI M27-A3 guidelines). If there is persistence or recurrence of vulvovaginal symptoms, additional vulvovaginal specimens will be collected for KOH testing at the TOC and at the FU visits, and for fungal culture at the FU visits. Samples will also be obtained at any unscheduled visit, if needed.

If the subject experiences persistence or worsening or recurrence of symptoms that per the investigator's assessment (e.g. symptoms ≥4) warrant the use of rescue antifungal therapy, the subject may be enrolled into Treatment Cycle 2 and receive additional treatment with ibrexafungerp for a period up to 14 days as recommended by the investigator and following discussion with the sponsor.

Whether or not a subject enters Treatment Cycle 2, or be prescribed rescue therapy, a vaginal examination with collection of samples for KOH (assess at the site) and culture should be completed prior to initiation of Treatment Cycle 2 or rescue therapy. If the KOH test is negative, the investigator should consider other causes for the persistence or worsening of the symptoms and antifungal rescue medication may not be indicated. If the collection of the vaginal culture is not possible prior to the initiation of the rescue therapy, it should still be collected as soon as possible after rescue therapy is given.

14.11. Rating of Vulvovaginal Signs by the Investigator Using the VSS Scale

The investigator (or qualified designee) will perform vulvovaginal examinations to rate the subject´s signs of infection at the Screening, TOC and first FU visits at 14 days after EOT. The vulvovaginal examination will be repeated at the rest of the FU visits only if the subject presents with symptoms. Otherwise, no additional vulvovaginal examination will be conducted, or signs rated. Vulvovaginal examinations may be conducted at unscheduled visits, if needed.

If the subject experiences persistence or worsening or recurrence of symptoms that per the investigator's assessment (e.g. symptoms ≥4) warrant the use of rescue antifungal therapy, the subject may be enrolled into Treatment Cycle 2 and receive additional treatment with ibrexafungerp for a period up to 14 days as recommended by the investigator and following discussion with the sponsor.

Whether or not a subject enters Treatment Cycle 2, or be prescribed rescue therapy, a vaginal examination with rating of signs by the investigator should be completed prior to initiation of rescue therapy. If the investigator's rating of the vulvovaginal signs is not possible prior to the initiation of the rescue therapy, it should still be completed as soon as possible after rescue therapy is initiated.

Investigators will assess the signs of infection using the VSS Scale provided in Section 21 [Appendix 2]), a standardized, predefined scale where each sign of the vagina and/or vulva will be given a numerical rating based on severity, as follows:

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

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

14.12. Quality of Life (QOL) Questionnaire

Subjects will complete a QOL questionnaire at Baseline, TOC and at the follow-up visits.

14.13. Randomization

This is an open label study. Subjects will be randomized to treatment and stratified by group based on the *Candida* species and presence or absence of underlying conditions.

14.14. Study Drug

At Baseline (Day 1), eligible subjects will have their Day 1 dose administered in the clinical research unit and will be dispensed enough study medication for either single day BID dose, or for BID dosing for 3 or 7 consecutive days as explained in Section 12.1.

14.15. Study Drug Dosing

Treatment Cycle 1 applicable to all subjects: The first study drug dose (Day 1) will be administered at the clinical research center and the subsequent dose(s) will be self-administered by the subjects at approximately 12 ± 3-hour intervals at home.

NOTE: 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 Day 1 doses at home to allow for a more convenient dosing schedule (e.g., 8 p.m. and 8 a.m.). Details of study treatment groups and dietary requirements for treatment administration are provided in Section 12.1 and Section 12.2, respectively.

Treatment Cycle 2: A second treatment cycle will be allowed for subjects who did not achieve sufficient clinical improvement (e.g. VSS remains ≥3) on the randomized treatment (Cycle 1) as evaluated at the TOC and FU1 visits. A second treatment cycle will also be allowed for subjects with clinical cure/improvement/success who experience a recurrence before the last FU visit.

During Cycle 2, subjects may receive additional treatment with ibrexafungerp for a period up to 14 days as recommended by the investigator and following discussion with the sponsor.

14.16. Study Drug Collection and Treatment Compliance Evaluation

Treatment compliance will be reviewed by the investigator or designee at the TOC visit. Subjects will be instructed to bring all blister packs (including empty blister packs) of study medication with them to the visit to assess treatment compliance. Further details are available in Section 12.5.

14.17. Vital Signs

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

14.18. Prior and Concomitant Medication Review

All medications (including prescription and over-the-counter medications, supplements, and herbal products) taken from 30 days before Screening visit through the TOC visit will be recorded in the eCRF. Only the use of other antifungal medications, medications used to treat vaginal infections, vaginal (topical) medications and antibiotics for any reason or any other medications to treat a study-drug related AE will be recorded after the TOC visit through the last study visit. Start and stop dates of concomitant medications will be recorded in the eCRF. Prior and concomitant medications will be reviewed and recorded at all scheduled and unscheduled study visits.

See Section 13.2 for prohibited medications, medications to be administered with caution and further details for non-study treatments.

14.19. Adverse Event Monitoring

AEs will be recorded and reviewed at all scheduled and unscheduled study visits from the time the ICF is signed through TOC visit. New AEs starting after TOC will be recorded only if they led to the use of other antifungal medications or topical vaginal treatment, if they are a vaginal bacterial or parasitic infection, or if they are deemed related to the previously administered study drug. See Section 16 for further reference.

15. STUDY SCHEDULE

Detailed schedules of all study visits and procedures are presented in Schedule of Visits and Procedures (Table 1).

The actual visits will be dependent on the Dosing Group i.e there may be overlapping visits.

Subjects entering Treatment Cycle 2, will follow the same Schedule of Visits and Procedures, starting with Baseline visit and may have visits that are Not Applicable during Treatment Cycle 1.

Table 1: Schedule of Visits and Procedures (Study SCY-078-307b)

Visit	V1 Screening[a]	V2 Baseline[a]	At Home	V3 TOC	V4 FU	V5 FU	V6 FU	V7 FU	Unscheduled Visits[b]
Day (allowable window)	Day -2(±1)	Day 1	Days 2-7	14 ±3 days post Baseline	14 ±3 days post EOT	30±4 days post Baseline	30 ±4 days post EOT	60 ±4 days post EOT	
Study Procedures									
Informed consent	X								
Enrollment and assignment of Subject ID number	X								
Inclusion/exclusion criteria[c]	X	X							
Medical history and demographics	X								
Abbreviated physical exam	X			X					If needed
Vital Signs[k]	X	X		X					If needed
Urine pregnancy test[c]	X			X					If needed
Safety laboratory blood tests[d]	X			X					If needed

Visit	V1 Screening[a]	V2 Baseline[a]	At Home	V3 TOC	V4 FU	V5 FU	V6 FU	V7 FU	Unscheduled Visits[b]
Day (allowable window)	**Day -2(±1)**	**Day 1**	**Days 2-7**	**14 ±3 days post Baseline**	**14 ±3 days post EOT**	**30±4 days post Baseline**	**30 ±4 days post EOT**	**60 ±4 days post EOT**	
Rating of vulvovaginal symptoms by the Subject[e]	X	X	X	X	X	X	X	X	If needed
Vaginal Examination and rating of vulvovaginal signs by the Investigator[e]	X			X	X	If symptoms	If symptoms	If symptoms	If needed
Vulvovaginal sample for other pathogens[e]	X			If needed	If needed	if needed	If needed	If needed	If needed
Vulvovaginal sample for KOH and pH [e]	X			If symptoms	If symptoms	If symptoms	If symptoms	If symptoms	If needed
Vulvovaginal sample for fungal culture[e]	X			X	X	If symptoms	If symptoms	If Symptoms	If needed
Quality of Life Questionnaire		X		X	X	X	X	X	
Study drug dosing		X	X						
Study drug container(s) collection and subject data reviewed				X					
Phone Contact[h]			X						
Prior and concomitant medication review[i]	X	X	X	X	X	X	X	X	X
AE monitoring[j]	X----------X				X	X	X	X	X

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

a) Screening and Baseline may occur on the same day.
b) Unscheduled visits can occur if the investigator determines there is a need for one outside of the scheduled per protocol visits.
c) Results should be reviewed prior to enrollment at Baseline (Day 1).
d) Hematology and blood chemistry. Safety laboratory tests will be performed by a qualified laboratory.
e) A vaginal examination with rating of signs by the investigator will be completed at the TOC visit. If the subject experiences persistence or worsening or recurrence of symptoms, after the baseline visit (e.g. symptoms ≥4), that warrant the use of rescue antifungal therapy, the symptoms that led to the use of rescue antifungal therapy must be documented in the eCRF. Additionally, vulvovaginal samples should be obtained for KOH testing and pH measurement (both at the clinical research unit), fungal culture (central laboratory) and investigation of other pathogens such as bacterial vaginosis and *Trichomonas vaginalis* (at the local lab). 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 visits only if the subject presents symptoms. Otherwise, no additional vulvovaginal examination will be conducted or signs rated.
g) The first study drug dose (Day 1) will be administered at the clinical research center and the subsequent dose(s) will be self-administered by the subjects at approximately 12 ± 3 hour intervals at home.
h) The Day 3, 5, and 7 phone contacts will be used to evaluate symptom resolution, AEs, and concomitant medications.
i) 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).
j) New AEs starting after TOC will be recorded only if they led to the use of other antifungal medications or topical vaginal treatment, if they are a vaginal bacterial or parasitic infection, or if they are deemed related to the previously administered study drug
k) Blood pressure (systolic and diastolic), heart rate and body temperature

16. SAFETY ASSESSMENTS AND MONITORING

16.1. Definition of an Adverse Event

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

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

Stable chronic conditions that are present prior to clinical trial enrollment and do not worsen are not considered AEs and will be accounted for in the subject's medical history.

The following can be considered AEs:

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event or condition
- A condition detected or diagnosed after the initiation of treatment with study medication, even though it may have been present prior to the start of the study
- Continuous persistent disease or symptoms present at baseline that worsen after signing the informed consent or following the initiation of treatment with study medication

The following are **not** considered AEs:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction or transfusion); the condition that leads to the procedure is an AE
- Pre-existing disease or conditions present or detected at the start of the study that do not worsen
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalizations for cosmetic surgery or elective surgery or social/convenience admissions)
- The disease being studied, or signs or symptoms associated with the disease, unless more severe than expected for the subject's condition or a worsening of the disease being studied

16.2. Definition of a Serious Adverse Event

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

- Death
- Life-threatening event
- Inpatient hospitalization or prolongation of existing hospitalization

- Persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly or birth defect

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

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

16.3. Events of Clinical Interest

Not Applicable

16.4. Overdose

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

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

16.5. Pregnancy

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

16.6. Unexpected Adverse Event

An AE is considered "unexpected" if it is not listed in the IB or is of greater specificity or severity than those that have been observed with the particular study drug being tested. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs that are

mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

16.7. Grading of Adverse Events

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

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

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

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

16.8. Causality Assessment

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

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

16.9. Adverse Event Collection Timeframe

AEs will be recorded and reviewed at all scheduled and unscheduled study visits from the time the ICF is signed through TOC visit. New AEs starting after TOC will be recorded only if they led to the use of other antifungal medications or topical vaginal treatment, if they are a vaginal bacterial or parasitic infection, or if they are deemed related to the previously administered study drug.

All AEs reported by the subject or observed by members of the clinical staff will be evaluated by the principal investigator (PI) or qualified designee. The PI will attempt, if possible, to establish a

diagnosis based on presenting signs and symptoms. The nature of the AE, time of onset relative to study drug administration, duration, severity, and relationship to treatment should be determined. Details of any corrective treatment must be recorded in the eCRF. The PI will determine whether any changes have occurred in baseline signs and symptoms. All AEs and SAEs will be collected in the eCRF.

16.10. Serious Adverse Event Reporting Requirements

All SAEs must be reported within 24 hours of the site becoming aware of the SAE (Appendix 3). Any event that is serious, study drug-related, and unexpected as assessed by the medical monitor or the Sponsor will be submitted to the regulatory authorities in accordance with national regulatory laws and regulations. The PI will be responsible for reporting all SAEs that require reporting to the local or central Institutional Review Board/Ethics Committee (IRB/EC) in accordance with its regulations and guidelines.

16.11. Adverse Event and Serious Adverse Event Follow-up

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

16.12. Serious Adverse Event Reporting – Procedures for Investigators

Initial Reports and Follow-Up SAE Reports: To report an SAE, the SAE eCRF form within the Electronic Data Capture (EDC) system must be completed. All SAEs, whether or not deemed drug-related or expected, must be reported by the investigator or qualified designee within 24 hours of first becoming aware of the event (Appendix 3). The investigator/qualified designee will enter the required information regarding the SAE into the appropriate form, which will automatically result in distribution of the information to the appropriate sponsor contact. If the EDC system is temporarily unavailable (>24 hours), the event, including the investigator-determined causality to study drug, should be reported via a paper back-up SAE form to the Safety Surveillance team via (contact information, i.e., e-mail or fax will be available on the SAE form).

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

17. DATA COLLECTION, STUDY MONITORING AND RECORD MANAGEMENT

17.1. Data Collection and Reporting

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

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

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

17.2. Study Monitoring

Study progress will be monitored by the Sponsor or its representative as frequently as necessary to ensure adequate and accurate data collection, protocol compliance, and study conduct in accordance with accepted regulatory requirements. The PI must make all the subject data available to the monitor for review during the planned site monitoring visits. Arrangements for monitoring visits will be made in advance, except in emergency cases.

17.3. Investigator Study Files

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

- original protocol and all amendments
- signed agreement or protocol
- signed and dated study staff roles and responsibilities log
- copy of the current *curriculum vitae* of the PI and of all sub-investigators
- IRB/EC membership list and all IRB/EC approvals for the protocol and amendments, informed consent documentation and all updates, advertisements, and written information provided to subjects; all IRB/EC correspondence; documentation that the IB and subsequent revisions have been submitted to the IRB/EC; documentation that all SAEs and any periodic safety reports have been submitted to the IRB/EC; and annual IRB/EC renewals (as required)
- updated laboratory certification and the laboratory's normal values (covering the entire time interval of the study for all laboratory tests conducted during the study)

- all confirmations of investigational drug receipt, drug accountability logs and drug return records
- all correspondence to or from the Sponsor or its designees
- blank informed consent form
- Investigator's Brochure
- subject screening log
- subject list (contains subject initials and/or protocol-specific subject number)
- all subjects' original signed informed consents
- monitoring visit log

17.4. Retention of Records

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

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

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

18. ANALYTICAL PLAN

All statistical processing will be performed using SAS® version 9.3 or later, unless otherwise stated. All statistical tests will be two-sided and interpreted at a 5% significance level.

The study is not powered for formal statistical comparisons. Descriptive statistics (i.e., mean, standard deviation, median, minimum, maximum, etc.) will be provided for all continuous variables; frequencies and percentages will be tabulated for incidence and categorical variables. For parameters measured over time, observed values and changes from baseline will be described for each time point.

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

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

A Statistical Analysis Plan (SAP) describing all statistical analyses in detail will be provided as a separate document. The SAP will be finalized prior to database lock.

18.1. Sample Size Determination

The primary efficacy endpoint of the study is the percentage of subjects with clinical cure (complete resolution of signs and symptoms with total composite score of 0 on the VSS Scale with no additional antifungal therapy required based on investigator's judgment) at the TOC visit. This is an exploratory study, and no formal sample size calculation was performed. Approximately 150 subjects will be enrolled in allocation 50:50:50 in respect of 1, 3 or 7 days of treatment. Subjects will be randomized to treatment, stratified by group based on the Candida species and presence or absence of underlying medical conditions. A sample size of 150 subjects is estimated to be adequate to perform an initial assessment of efficacy.

18.2. Analysis Populations

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

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

Modified Intent-to-Treat (MITT) Population: All treated subjects who have a positive culture for *Candida species* at Screening.

Per-Protocol (PP) Population: All MITT subjects who have completed the study drug treatment, who did not have major protocol deviations likely to affect study efficacy AND who have a TOC evaluation.

Safety Population: All enrolled subjects who received at least one dose of study drug.

18.3. Subject Disposition, Discontinuation, and Baseline Data

Subject disposition in terms of the number and percentage of subjects enrolled by site will be tabulated. The number of subjects enrolled, number completing the study, and reasons for discontinuation will be summarized by treatment group. Subject demographics and baseline characteristics such as age, race, ethnicity, sex, weight, height, body mass index, region (if applicable) and other relevant parameters will be tabulated by treatment group.

Baseline is defined as the last non-missing assessment prior to the date (and time if appropriate) of the first dose of study drug. Change from baseline is defined as: post- baseline value – baseline value.

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

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

18.5. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary terminology. The number and percentage of subjects taking each medication before and after the first dose of study drug will be tabulated by treatment group. Medications taken and stopped prior to the first dose of study drug will be considered prior medications. Medications

started on or before the FU visit date with missing start dates or stop dates after the first dose of study drug will be considered concomitant medications.

18.6. Efficacy

18.6.1. Efficacy Assessments

Efficacy assessments will be based on VSS scores, clinical evaluations, QOL outcomes, mycological testing, and additional antifungal use by the TOC visit and FU visits.

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

- Clinical Cure: Complete resolution of signs and symptoms with total composite score of 0 on the VSS Scale and with no additional antifungal therapy required based on investigator's judgment
- Clinical Improvement: partial resolution of signs and symptoms with total composite score of 1 or 2 on the VSS Scale and with no additional antifungal therapy required based on investigator's judgement.
- Clinical Success: at least 50% reduction from Baseline in the total composite VSS score with no additional antifungal therapy required based on investigator's judgment
- Clinical Failure: Persistence and/or worsening of signs and symptoms or need for additional antifungal therapy

18.6.1.2. Mycological Outcome

- Mycological Eradication: negative culture for growth of *Candida* species
- Presumed Eradication: Subject is asymptomatic, therefore cultures not done
- Mycological Persistence: positive culture for growth of *Candida* species

18.6.2. Efficacy Analyses

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

The primary efficacy endpoint, the percentage of subjects with Clinical Cure at TOC will be assessed on the MITT population and will present the Clinical Success rate and the 95% confidence interval calculated using the method of Clopper and Pearson. All other efficacy data will be summarized, but not subject to formal statistical analysis.

18.7. Safety

18.7.1. Safety Assessments

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

AEs will be recorded and reviewed at all scheduled and unscheduled study visits from the time the Informed Consent Form is signed. An abbreviated physical examination, including general appearance and an overall examination of body systems, will be conducted at Screening, at the TOC visit and at the first FU (14 Days after EOT) visit. Vital signs, including blood pressure (systolic and diastolic), heart rate, respiratory rate and body temperature will be measured at the Screening and TOC visits and at unscheduled visits, if needed. Safety laboratory test (hematology and blood chemistry) will be measured at Screening, at the TOC visits and at unscheduled visits, if needed. All prior and concomitant medications taken before Screening 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.

Study procedures are described in Section 14.0 and safety assessments and monitoring are described in Section 16.0.

18.7.2. Safety Analyses

Safety analyses will be conducted using the safety population.

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

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

19. ETHICS AND PROTECTION OF HUMAN PATIENTS

19.1. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, the ethical principles established by the Declaration of Helsinki (as amended in Fortaleza, Brazil, October 2013), the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines, the US Code of Federal Regulations (CFR) sections that address clinical research studies, applicable European Union regulations and/or other national and local ethical and legal requirements, as applicable.

19.2. Institutional Review Board/Ethics Committee Review

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

19.3. Informed Consent

The ICH issued guidelines to provide protection for human subjects in clinical investigations. The ICH Tripartite Guideline for Good Clinical Practice establishes the general requirements for informed consent. Each subject will be provided with oral and written information in a language they can understand that describes the nature and duration of the study. Before undergoing screening, each subject must consent in writing to study participation. The patient will sign and personally date the subject ICF. The person rendering consent will also sign and personally date the subject ICF as the person who obtained the consent of the subject. The original signed subject ICF will be retained with the study center's records. Each subject will receive a copy of her signed subject ICF. In addition, the PI, or his or her designee, must document in the case history that informed consent was obtained before study participation.

19.4. Future Use of Samples

Biological samples collected during the study, including *Candida* spp. isolates (see Section 14.9 and Section 14.10), may be maintained in repositories for potential future use. Future research of *Candida* isolates may include *in vitro* susceptibility testing of new or existing antifungals or analysis of mechanisms of resistance. All samples will be identified only by a coded number to maintain subject confidentiality.

19.5. Subject Privacy and Subject Confidentiality

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

19.6. Study Termination

The PI, the sponsor, the FDA, and the IRB/EC each reserve the right to terminate the study in the interest of subjects' safety and welfare. The sponsor reserves the right to terminate the study at any time for administrative reasons. The sponsor also reserves the right to discontinue study enrolment if a particular cohort is proving difficult to enroll.

19.7. Financial Disclosure

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

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8) Scorneaux B, Angulo D, Borroto-Esoda K, Ghannoum M, Peel M, Wring S. SCY-078 Is fungicidal against *Candida* species in Time-Kill studies. Antimicrobial Agents and Chemotherapy 2017 March;61(3):e01961-16.

9) Arendrup MC, Jorgensen KM, Hare RK, Chowdhary A. *In vitro* activity of ibrexafungerp (SCY-078) against *Candida auris* isolates as determined by EUCAST methodology and comparison with activity against *C. albicans* and *C glabrata* and with the activities of six comparator agents. Antimicrobial Agents and Chemotherapy 2020 March;64(3):202136-19.

10) Sobel JD, Borroto-Esoda K, Azie N, Angulo D. *In vitro* pH activity of ibrexafungerp against fluconazole-susceptible and -resistant *Candida* isolates from women with vulvovaginal candidiasis. Antimicrobial Agents Chemotherapy 2021 May doi:10.1128/AAC.00562-21.

21. APPENDICES

APPENDIX 1. PROHIBITED MEDICATIONS AND MEDICATIONS TO BE ADMINISTERED WITH CAUTION

Prohibited Medications

The use of any topical vaginal corticoids and topical vaginal contraceptives is prohibited during the study. No systemic or topical vaginal antifungal treatment other than the study drug is allowed during the study unless used as rescue medication after the subject has been documented as not responding to study drug. No investigational drugs other than the study drug are allowed within 30 days before Screening and for the entire duration of the study. In addition, the medications listed below are also prohibited.

Strong CYP3A4/5 inhibitors and CYP3A4/5 inducers

CYP	Strong Inhibitors[a]	Inducers[a]
3A4/5	Ketoconazole Itraconazole	bosentan carbamazepine phenytoin rifampin St. John's wort long-lasting barbiturates efavirenz etravirine

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

Medications to be administered with Caution and Monitored as Appropriate

CYP3A4 substrates

CYP	Substrates
3A4	*In vitro*, ibrexafungerp (SCY-078) was an inhibitor of CYP3A mediated metabolism of midazolam, but was only a weak inhibitor of metabolism of testosterone. The clinical significance of this inhibition is unknown; caution should be exercised when administering ibrexafungerp (SCY-078) with drugs known to be CYP3A sensitive substrates with narrow therapeutic index, such as midazolam and cyclosporine. Subjects receiving sirolimus, tacrolimus, warfarin, cyclosporine or amiodarone are permitted for enrollment in the study and these medications may be administered concomitantly with ibrexafungerp (SCY-078) with close monitoring. Dosing adjustments and subsequent monitoring of sirolimus and warfarin should be undertaken in accordance with product prescribing information for the respective agents.

OATP1B3 substrates

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

P-gp Drug Substrates
digoxin, colchicine, dabigatran

Sources:

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

APPENDIX 2. VULVOVAGINAL SIGNS AND SYMPTOMS SCALE

SIGNS:

To be rated by the investigator during the vulvovaginal examination

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

- Definitions: Absent: none Mild: slight
- Moderate: definitely noticeable Severe: marked, intense

SYMPTOMS:

To be rated by the subject

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

Definitions:

- Absent: I have no discomfort (i.e., burning, itching, irritation)
- Mild: I have some discomfort (i.e., burning, itching, irritation), but it does not bother me much
- Moderate: I have discomfort (i.e., burning, itching, irritation), which is annoying, but not enough to affect what I am doing
- Severe: I have discomfort (i.e., burning, itching, irritation), which is annoying enough to affect what I am doing

APPENDIX 3. SERIOUS ADVERSE EVENT REPORTING

SAEs, as defined in Section16 Safety Assessments and Monitoring will be reported in accordance with ICH E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

Site Responsibilities

All SAEs that occur during the course of the study must be reported to SCYNEXIS within 24 hours of the knowledge of the occurrence.

The Investigator will fill out the SAE form and provide as complete information as are available. At a minimum, subject number, the dates and times of the study drug administered, a narrative description of the event must be provided. An assessment by the Investigator as to the severity of the event and relatedness to study drug should also be provided, if possible. Investigator will report all SAEs to:

SCYNEXIS Inc.
1 Evertrust Plaza, 13th Floor
Jersey City, NJ 07302
SAE@SCYNEXIS.com
and
safety.scynexis@awinsals.com Telephone: +1.760.372.7230 Fax: +1.844.769.3213

The investigator will report SAE and any follow up information to the Research Ethics Board (REB) per REB procedures and requirements.

The investigator will provide SAE follow-up information as soon as information is available to SCYNEXIS.

SCYNEXIS Responsibilities

If the SAE is considered a Suspected, Unexpected Serious Adverse Reaction (SUSAR) SCYNEXIS or designee will create a CIOMS or a Medwatch 3500A Report for submission to the relevant regulatory authority within 15-days after SCYNEXIS has learned of the SAE. If the SUSAR is a fatal or life-threatening event, the reports will be sent within 7 days after SCYNEXIS has learned of the event.

Follow-up reports will be provided to regulatory agencies as soon as information is available according to the same reporting periods.

APPENDIX 4. PROTOCOL REVISION HISTORY

Revisions to Protocol dated 12 October 2021 (Protocol Version 2.0)
Current Version and Date: Protocol Amendment 2 (Protocol Version 3.0) dated 17 January 2022

Amended to delete the ~~strikethrough~~ text and include the **bolded** text

Protocol Section	Change and *Rationale*
	- **Definition of "Clinical Cure" changed from a total composite score on the VSS Scale of "≤ 2" to "0".** ***In response to FDA comments*** - **Addition of "Clinical Improvement" as another Clinical Outcome and Secondary Endpoint.** ***Follow-on to above change***
Synopsis: Study Endpoints Synopsis: Statistical Analysis Section 9.1: Primary Endpoint Section 9.2: Secondary Endpoints Section 18.6.1.: Efficacy Assessments	Clinical Outcomes: Clinical Cure: ~~partial or~~ Complete resolution of signs and symptoms with total composite score of ~~≤ 2~~ **0** on the VSS Scale and with no additional antifungal therapy required based on investigator's judgment. **Clinical Improvement: partial resolution of signs and symptoms with total composite score of 1 or 2 on the VSS Scale and with no additional antifungal therapy required based on investigator's judgement.** Efficacy as measured by: **The percentage of subjects with clinical improvement** **– Total composite score of 2 on the VSS Scale at the TOC and Follow-up (FU) visits.** **– Total composite score of 1 on the VSS Scale at the TOC and FU visits.**
Synopsis: Study Visits Section 6: Schematic of Study Design Section 10.1.1: Study Visits Section 14: Study Procedures Section 15: Study Schedule	**Changes to Study Visits:** ***In response to FDA comments*** - **TOC visit was changed from 14 days *after EOT* to *14 days after Baseline*** - **FU Visit 14 (±3) days after EOT was added** - **FU visit 30 (±3) days after Baseline was added** **STUDY VISITS:** The study will consist of a Screening visit on Day -2 (±1), Baseline visit on Day 1 (if applicable, the Screening and Baseline visits can both be done on Day 1), Phone contacts on Days 3, 5 and 7 (±1), a TOC visit 14 (±3) days **after ~~EOT~~ Baseline** and FU visits at**: 14 days (±3) days after End Of Treatment (EOT), 30 (±4) after Baseline,** 30 (±4) days after EOT and 60 (±4) days after EOT. TOC visit (14 days [±3] after ~~EOT~~ **Baseline**): At this visit…. **FU visit (14 days [±3] after EOT): At this visit, treatment compliance will be reviewed and any AEs and/or concomitant medications evaluated. The investigators and the subjects will again rate the signs and symptoms of infection on the VSS Scale and the subjects will complete a QOL questionnaire. Vulvovaginal samples for fungal culture, species identification, and antifungal susceptibility testing will be obtained and sent to a designated central laboratory. Additional vaginal samples will be obtained for a KOH test and vaginal pH measurement by the local laboratory if symptoms persist or have worsened.** FU visits: **30 (±4) days after Baseline**, 30 (±4) days after EOT and 60 (±4) days after EOT: At the FU visits….

<table>
<tr><td>Synopsis

Section 10.1. Overall Description of the Study

Section 10.2 Blinding, Randomization and Stratification

Section 14.13 Randomization</td><td><u>Study design changed from non-randomized without stratification, to randomized with stratification.</u> In response to FDA comments

STUDY BLINDING, RANDOMIZATION, AND STRATIFICATION: This is an open-label study. <s>There will be no blinding, randomization, or stratification.</s> Subjects will be randomized to treatment, stratified by group based on the Candida species and presence or absence of underlying medical conditions.

Approximately <s>100</s> 150 eligible subjects will be enrolled. Subjects will be randomized to receive oral ibrexafungerp 300 mg administered twice a day (BID) for either one, three, or seven consecutive days, stratified by group based on Candida species and presence or absence of underlying medical conditions.</td></tr>
<tr><td>Synopsis

Section 18.1: Sample size Determination</td><td><u>Sample size increased from 100 to 150 subjects to be enrolled.</u> Impact of response to FDA comments

Sample Size Determination:

The primary efficacy endpoint of the study is the percentage of subjects with clinical cure (<s>partial or</s> complete resolution of signs and symptoms with total composite score <s>≤2</s> of 0 on the VSS Scale with no additional antifungal therapy required based on investigator’s judgment) at the TOC visit. <s>As this is a single arm, a statement regardingCI) will be produced. It is estimated that 100 eligible subjects will be enrolled.</s>

This is an exploratory study, and no formal sample size calculation was performed. Approximately 150 subjects will be enrolled in allocation 50:50:50 in respect of 1, 3 or 7 days of treatment. Subjects will be randomized to treatment, stratified by group based on the Candida species and presence or absence of underlying medical conditions. A sample size of 150 subjects is estimated to be adequate to perform an initial assessment of efficacy.</td></tr>
<tr><td>Synopsis

Section 10.3: Study Duration

Section 12.1: Study Treatment Groups

Section 12.4.: Ibrexafungerp Description

Section 12.5.: Drug accountability

Section 14: Study Procedures</td><td>- <u>Treatment Groups changed from 3 groups to 2 groups (Treatment Cycle 1).</u> To simplify
- <u>Added potential for additional Treatment Cycle 2 treatment.</u> To provide additional treatment option to patients with inadequate response
- <u>Study duration increased to potentially 130 days.</u> As a result of the addition of Treatment Cycle 2
- <u>IP will be provided in blister packs. Changed from bottles.</u> Company logistics

Ibrexafungerp Treatment Groups:

<table>
<tr><th>Treatment Group</th><th>Criteria</th><th>*Ibrexafungerp Dose (300mg AM and 300mg PM) Randomization and Stratification</th></tr>
<tr><td>Group A</td><td><s>Subjects who do not fit criteria for Groups B and C</s>
Subjects without underlying medical conditions AND known to have isolates other than C glabrata, C krusei, C auris</td><td>1 Day dosing
N=50</td></tr>
<tr><td>Group B</td><td>Subjects with underlying medical conditions: DM, immunocompromised conditions (e.g. HIV), debilitation, immunosuppressive therapy (e.g. corticosteroids), recurrent VVC (≥3 episodes/year) AND/ OR known to have C glabrata, C krusei or C auris isolates</td><td>3 Day OR 7 Days dosing
Randomized 1:1
N=50:50</td></tr>
<tr><td><s>Group C</s></td><td><s>Subjects known to have C glabrata, C krusei or C auris isolates</s></td><td><s>7 Day dosing</s></td></tr>
</table>
</td></tr>
</table>

	***Days of treatment is per CDC Guidelines (https://www.cdc.gov/std/treatment-guidelines/candidiasis.htm)** **Enrollment will continue until the target number in each cohort is reached.** **Treatment Cycle 2: A second treatment cycle will be allowed for subjects who did not achieve sufficient clinical improvement (e.g. VSS remains ≥3) on the randomized treatment (Cycle 1) as evaluated at the TOC visit or at the FU EOT+14 visits. A second treatment cycle will also be allowed for subjects with clinical cure/improvement/success who experience a recurrence before the last FU visit. During Cycle 2, subjects may receive additional treatment with ibrexafungerp for a period up to 14 days as recommended by the investigator and following discussion with the sponsor.** Study Duration: Each subject is expected to complete the study in approximately 65 days **and up to approximately 130 days for subjects who require additional treatment and enter Treatment Cycle 2.** **Oral tablets will be supplied in blister packs of four 150 mg tablets per blister. Each blister constitutes one day's dosing of 300 mg BID.**
Section 16.3: Events of Clinical Interest	**Events of Clinical Interest – Removed.** ***No longer required since Ibrexafungerp safety profile is well established*** 16.3. Events of Clinical Interest - **Not Applicable** ~~The following are considered events of clinical interest (ECIs) if they occur after dosing, and must be reported by the site when it becomes aware of the ECI:~~ ~~• ALT or AST > 8 x the upper limit of normal (ULN), confirmed by repeat testing~~ ~~• ALT or AST > 5 x ULN for more than 2 weeks if new compared to Baseline, confirmed by repeat testing~~ ~~• ALT or AST > 3 x ULN and total bilirubin >2 x ULN if new compared to Baseline, confirmed by repeat testing~~ ~~• ALT or AST > 3 x ULN, confirmed by repeat test, with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)~~

Revisions to Protocol dated 03 September 2021 (Protocol Version 1.0) Current Version and Date: Protocol Amendment 1 (Protocol Version 2.0) dated 12 October 2021.	
Protocol Section	**Change and Rationale**
Section 4. Revision History	This section is added to track revisions to the protocol. Numbering of sections changed throughout.
Section 6 Protocol Synopsis Section 7 Schematic of Study Design Section 9 Study Objectives Section 10 Study Endpoints Section 11.1 Study Visits Section 11.2 Study Assessments Section 15.12 Quality of Life Questionnaire Section 19.6.1 Efficacy Analysis	Add text that the Quality of Life Questionnaire will be completed at Baseline, TOC and Follow-up visits to sections where it was previously omitted.
Section 12.2 Inclusion Criteria	**Add text to clarify the pregnancy prevention requirements as part of Inclusion Criteria** "Subject is not pregnant or lactating and plans not to become pregnant. Women of childbearing potential < 1 year post-menopausal must agree to and comply with using one barrier method (male condom, female condom, and diaphragm) plus one other highly effective method of birth control, or sexual abstinence, from the time of consent through 10 days after the completion of study therapy."