Statistical Analysis Plan

Study Protocol Number: SCY-078-307b

Study Title:

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

NCT05399641

Study Sponsor:

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1. Signature Page

Authors

The undersigned have reviewed and approved the statistical analysis plan and find the document to be consistent with the requirements of the Protocol.

_____ _____
Date

Approval

The undersigned have reviewed and approved the statistical analysis plan and find the document to be consistent with the requirements of the Protocol.

_____ _____
President & Chief Executive Officer
SCYNEXIS, Inc.
Date

2. Abbreviations

Abbreviation	Definition
AE	Adverse event
ATC	Anatomical Therapeutic Class

Abbreviation	Definition
BID	Twice a Day
BMI	Body Mass Index
CRF	Case report form
EOT	End of therapy
FU	Follow Up
HIV	Human immunodeficiency virus
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified Intent-to-Treat
PP	Per-Protocol
PT	Preferred term
QOL	Quality of Life
SAP	Statistical analysis plan
SAE	Serious adverse event
SD	Standard deviation
SOC	System organ class
TEAE	Treatment-emergent adverse event
TFLs	Tables, figures, and listings
TOC	Test of Cure
VVC	Complicated Vulvovaginal Candidiasis
VSS	Vulvovaginal Signs and Symptoms Scale
WHODrug	World Health Organization Drug Enhanced Dictionary

3. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the procedures and statistical methodologies that will be used in the analysis and reporting of results for SCYNEXIS, Inc. Protocol SCY-078-307b.

This document is prepared based on the following documents:

- the study protocol version 3.0 dated 17 January 2022.
- the case report form (CRF) version 1.2 dated 9 September 2022.

Readers are referred to the final study protocol, the CRF, and CRF completion guidelines for details of the study design, conduct and data collection. This SAP must be finalized prior to the locking of the clinical database for this study. The mock tables, figures, and patient data listings (TFLs) are provided in a separate document.

4. Objectives and Endpoints

4.1. Objectives

4.1.1. Primary Objectives

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

4.1.2. 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.

4.1.3. Exploratory Objectives

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

4.2. Endpoints

4.2.1. Primary Endpoints

- Efficacy as measured by the percentage of subjects with clinical cure (total composite score of 0 on the VSS Scale (refer to Appendix 1) with no additional antifungal therapy required based on investigator's judgment) at the TOC visit.

4.2.2. 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 total composite score equal or less than 2 and equal or less than 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.

5. Study Design

5.1. Study Design Overview

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.

5.2. Study Schedule

The scheduled assessments will be carried out as described in Section 15 of the study protocol.

5.3. Randomization and Blinding

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.

5.4. Sample Size

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.

6. Statistical Analyses

6.1. General Considerations

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 it is with no imputation. No adjustment for multiplicity will be employed.

This Statistical Analysis Plan (SAP) will describe all statistical analyses in detail. The SAP will be finalized prior to database lock.

6.1.1. Baseline and Change from Baseline Definition

Baseline is defined as the last assessment prior to the first dose of study drug. If time and date are available, then the baseline assessment could be on the same day as first dose so long as it's before the time of first dose. If time is not available, the date prior to first dose will need to be used. Change from baseline is defined as: non-missing post- baseline value – baseline value. Baseline values will be re-calculated in Cycle 2 for QOL scale, VVS composite score, physical examinations, lab results and vital signs. If above baseline value is not available in Cycle 2, then use the last available value in Cycle 1 as baseline for Cycle 2.

6.1.2. Missing Data Handling

No imputation of missing data will be performed unless otherwise specified.

The following rules will be used to impute partial dates for AE or concomitant medications:

- Partial start dates:
    - If only the day of the month is missing:
      The onset date will be set to the first day of the month unless the month is the same as the first dose, where the onset date will be set to the date of the first dose date. However, if this

imputation leads to an onset date later than the end date of the event, the start date will still be set as the first day of the month.

- If both the day and month are missing:
  The day and month will be assumed to be January 1 of the year, unless the event occurred in the same year as the first dose, where the start date will be set to the day of the first dose. However, if this imputation leads to an onset date later than the end date of the event, the start date will still be set as January 1 of the year.
- If the start date is completely missing:
  The missing start date will be set to the date of the first dose. However, if this imputation leads to an onset date later than the end date of the event, the start date will be set to the first day of the month/year of the end date.

- Partial end dates:
  - If only the day is missing: the end date will be set to the last day of the month or the last follow-up date whichever earlier.
  - If both the day and the month are missing: the end date will be set to December 31 or the last follow-up date whichever earlier.
  - If the end date is completely missing: no imputation will be implemented.

6.2. 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.

6.3. Demographics and Study Summary

6.3.1. Patient Disposition

The number of subjects enrolled, number completing the study, and reasons for discontinuation will be summarized by treatment group and by cycle.

6.3.2. Eligibility and Protocol Deviations

Eligibility status based upon meeting protocol entrance criteria (ex: resistant/intolerant/prophylaxis failures, etc.) and protocol deviations will be listed by subject. Protocol deviations recorded will be reviewed and major deviations will be identified prior to database lock. The PP population will be determined and subjects with major protocol violations, entry criteria violations or missing visits will be excluded.

6.3.3. Demographics and Baseline Characteristics

Demographic/baseline characteristics collected at the Screening/Day 1 visit will be summarized and presented for each treatment group. Descriptive statistics will be presented for the continuous variables. Frequency counts and percentages will be presented for the categorical variables for each category. The following variables will be presented:

- Demographic characteristics (*Screening)*
    - Age (years)
    - Sex (male, female)
    - Race
    - Ethnicity
    - Height (cm)
    - Weight (kg)
    - BMI (kg/m^2)
- Vulvovaginal Examination (*Screening)*
- QOL questionnaire (*Day 1*)
- Fertility Status

- Surgically Sterile / Infertile
- Post-Menopausal
- Potentially Able to Bear Children

- Method of Birth Control
  - Oral Contraceptives
  - Depo Contraceptives (Implants / Injectables)

6.3.4. Medical History

Medical history terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA 26.0) dictionary. All the medical history will be summarized by system organ class (SOC) term and preferred term for each cohort by treatment group. For subjects with the same SOC and preferred term occurring more than once, the first occurrence will be tabulated. Medical history events will be sorted alphabetically by SOC and within each SOC, the PT will be presented by decreasing order of total frequencies.

Conditions will be listed, including the verbatim investigator description of the relevant medical condition, the coded terms (SOC, preferred term), start date, end date, and whether the condition is ongoing.

6.3.5. Prior and Concomitant Medications

Prior medications are defined as any medication started and discontinued prior to the first dose of study treatment. Concomitant medications are defined as any medication taken on or after the first dose of study treatment, including those who started prior to the date of the first dose of study treatment and continued past that date. See section 7.1.3 for handling of completely or partially missing dates for prior and concomitant medications.

6.3.6. Study Drug Administration

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 into 2 groups 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 TABLE 1:

Table 1: Ibrexafungerp Treatment Groups

Treatment Group	Criteria	Ibrexafungerp Dose 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 (300mg AM and 300mg PM) 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 (300mg AM and 300mg PM) Randomized 1:1 N = 50:50

6.4. Efficacy Analyses Cycle 1

The efficacy analyses will be conducted using the MITT (primary analysis population), ITT and PP populations to evaluate ibrexafungerp. Efficacy outcomes will be presented by treatment group in Cycle 1.

6.4.1. Primary Efficacy Analysis

6.4.1.1. Definition of Primary Endpoint

The primary efficacy endpoint is 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.

6.4.1.2. Main Analysis Approach

Clopper-Pearson method will be used to summarize 95% CI of proportion of clinical cure for group A and group B separately. Pairwise treatment comparison of subjects in group B 3 days vs. subjects in group B 7 days will be performed to test primary efficacy endpoint (clinical cure at TOC visit) using a Fisher's Exact

test; p-values and 95% confidence intervals for odds ratio will be presented. The primary endpoint will also be analyzed of subjects in group B 3 days vs. subjects in group B 7 days using a Cochran-Mantel-Haenszel row mean scores test stratified by site.

VSS scores at Baseline, TOC, and FU will be summarized for each sign and symptom using frequency counts and percentages.

Summary statistics will be provided for the total VSS composite score (observed value and change from baseline). Student's t-test will be used for pairwise treatment comparison of subjects in group B 3 days vs. subjects in group B 7 days; p-values and 95% confidence intervals will be presented for the differences between treatment groups.

6.4.2. Secondary Efficacy Analyses

6.4.2.1. Definition of Secondary Endpoint

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 (this definition also applies to cycle 2 patients).

The following mycological outcome definitions will be used for the assessment of subjects with mycological response.

• 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.

6.4.2.2. Main Analysis Approach

Frequency and percentage of subjects with total composite score equal or less than 2 on the VSS scale at the TOC and FU visits, and total composite score equal or less than 1 on the VSS scale at the TOC and FU visits will be summarized.

Frequency and percentage of subjects with clinical improvement, clinical success, mycological response, with both clinical cure and mycological response at TOC and FU visit, with clinical cure at FU visit will be summarized.

The value and absolute change in total composite VSS score from baseline to the TOC and FU visits will be summarized with descriptive statistics.

6.4.3. Exploratory Efficacy Analyses

6.4.3.1. Definition of Exploratory Endpoints

The Quality-of-Life Questionnaire (QOL) used was developed by SCYNEXIS to measure the absolute change from Baseline in 6 VVC symptoms. Each symptom was measured on a 10-point visual analog scale (0 being None and 10 being Extreme) from patient recall over the preceding week. In addition, two questions were included on Patient Global Impression of Change (PGIC) to measure changes in overall health and overall sexual satisfaction since study start. Ratings were on a scale of 1 (Very much improved) to 7 (Very much worse).

Time to resolution of symptom is defined as the time from initiation of study treatment until resolution of the symptom, which is measured by VSS score = 0. The data will be collected from initiation of study treatment to last FU visit in Cycle 1 and Cycle 2 separately. Time to resolution of any symptom and time to resolution of all symptoms will be summarized by treatment for subjects in MITT, ITT and PP population.

6.4.3.2. Main Analysis Approach

The value and absolute change in QOL score from baseline to the TOC and FU visits will be summarized with descriptive statistics for each symptom by visit. The value and absolute change of mean score of QOL questions (excluding PGIC) from baseline to the TOC and FU visits will be summarized with descriptive statistics by visit. Proportion and 95% CI of each category will be summarized using Clopper-Pearson method for 2 PGIC questions by visit.

Time to resolution of signs and symptoms after initiation of study drug will be analyzed using Kaplan-Meier methods. Median survival time at which half of the subjects had reached resolution of symptoms and its 95% CI will be reported using Brookmeyer-Crowley method. Pairwise treatment comparisons of subjects in group B 3 days vs. subjects in group B 7 days will be performed using log-rank test.

6.4.3.3. Additional Estimates

For the subgroup analyses by Candida species, only descriptive statistics will be provided; no statistical testing will be performed due to possible small sample size.

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

6.5 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.

6.5.1. Efficacy Analysis (Treatment Cycle 2)

The proportion of Cycle 2 subjects enrolled in MITT, ITT and PP populations will be summarized in each table.
Secondary, and exploratory efficacy analysis will be analyzed the same as for cycle 1.

6.6. Safety Analyses

6.6.1. Adverse Events

A Treatment-emergent adverse event (TEAE) is defined as any AE that occurs on or after the start time of the study drug administration. AEs will be coded using the MedDRA 26.0 dictionary.
A summary of TEAEs will be presented as the number and percentage of subjects with at least one of the following:

- Any AE
- Any TEAE

- Treatment-related TEAE
- Serious TEAE
- Treatment-related serious TEAE
- TEAE leading to study drug withdrawal
- TEAE leading to death

TEAEs will be summarized by SOC and preferred term for each treatment group. For subjects with the same SOC and preferred term occurring more than once, the first occurrence will be tabulated. TEAEs will also be presented for each preferred term by maximum severity, by highest relationship to study drug, and for serious AEs. In the overall summary, additionally, the number and percentage of patients with at least one severe TEAE, with at least one moderate TEAE but no severe TEAE and with only mild TEAEs will be provided.

6.6.2. Clinical Laboratory Assessments

Laboratory data will be presented as per the international system of units, universally abbreviated as SI (from the French 'system international').

Hematology and blood chemistry will be summarized using descriptive statistics by treatment group and visit. Change from baseline values will be summarized similarly by treatment group for each post-baseline scheduled visit. Number and percentage of subjects with urine pregnancy test will be provided by treatment group and visit.

Shift tables from baseline to post-baseline for hematology and blood chemistry assessment, describing shifts to abnormality (low, normal, or high), will be provided. The number of subjects with a non-missing result at both baseline and a specific post-baseline scheduled visit will be used as denominator for that post-baseline scheduled visit.

Separate listings of all hematology, blood chemistry and urine pregnancy data will be provided. In addition, separate listings for hematology, blood chemistry, and urine pregnancy data will be provided for each parameter where a subject had at least one abnormal result.

All laboratory tests required at screening and/or baseline only will be listed.

6.6.3. Physical Examinations and Clinical Assessment of Signs and Symptoms

Physical Examination will be presented in a subject listing, with abnormal values flagged and abnormal description listed if any. Clinical assessment of signs and symptoms at each visit will be summarized and listed by subject.

6.7. Patient Profile

Patient profile will be provided for all subjects. Please refer to the separate patient profile sample document.

7. APPENDIX 1: 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:

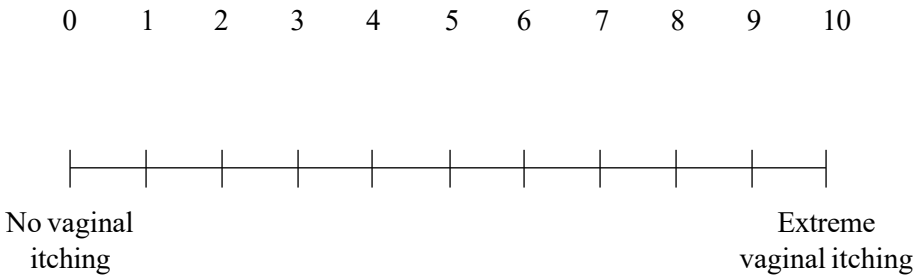
- Absent: I have no discomfort (i.e., burning, itching, irritation)
- Mild: I have some discomfort (i.e., burning, itching, irritation), but it does not bother me much
- Moderate: I have discomfort (i.e., burning, itching, irritation), which is annoying, but not enough to affect what I am doing
- Severe: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

8. APPENDIX 2: QUALITY OF LIFE

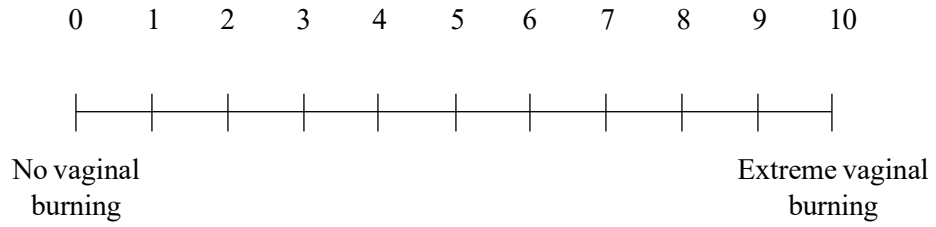
8.1. SECTION 1

The following questions ask about your VVC symptoms and their impact on your overall wellness. Please indicate with a cross on the line below how you would rate your symptoms over the past **7 days**.

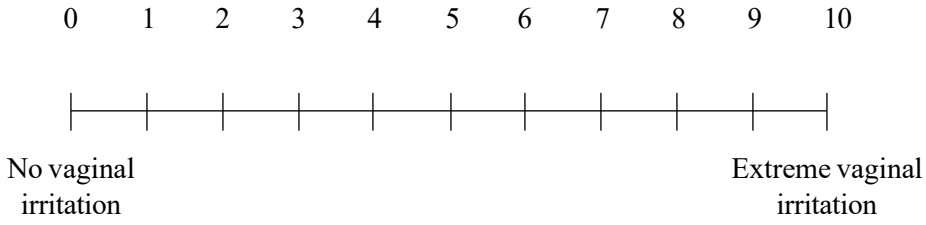
1. How would you rate your vaginal itching over the past 7 days?



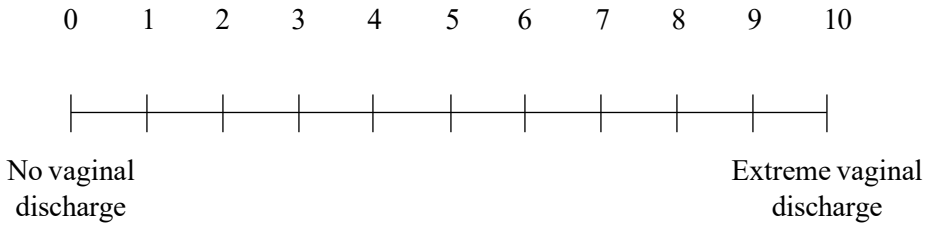
2. How would you rate your vaginal burning over the past 7 days?



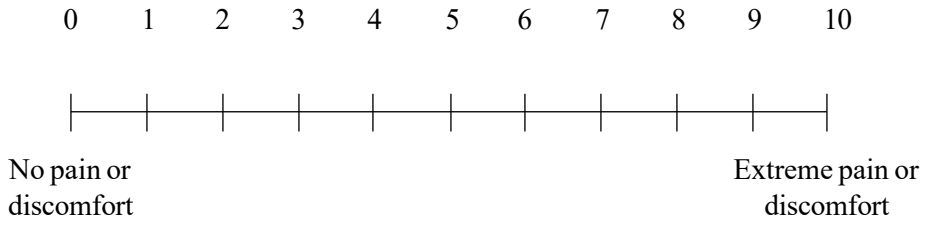
3. How would you rate your vaginal irritation over the past 7 days?



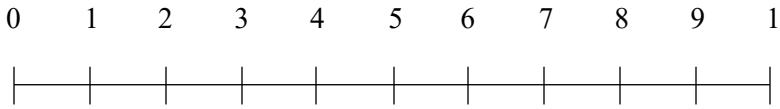
4. How would you rate your vaginal discharge over the past 7 days?



5. How would you rate your pain or discomfort during urination over the past 7 days?



6. How would you rate your pain or discomfort during sexual intercourse over the last 7 days?

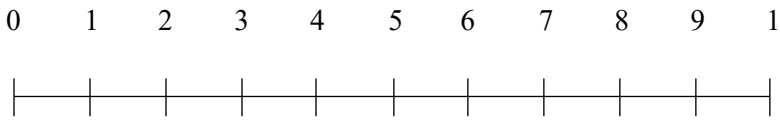


Δ **Not Applicable (N/A)**

No pain or discomfort

Extreme pain or discomfort

7. To what extent have your VVC symptoms affected your willingness to engage in sexual intercourse over the last 7 days?

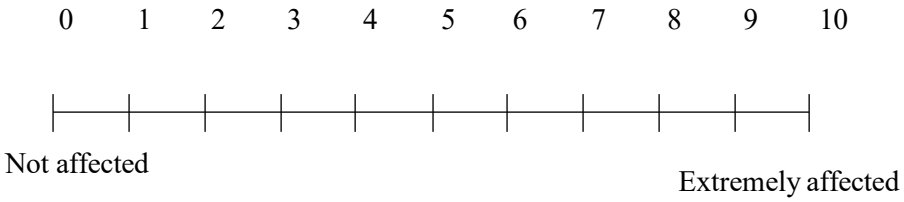


Δ **Not Applicable (N/A)**

Not affected

Extremely affected

8. To what extent have your VVC symptoms affected your overall mood; for example, feeling anxious and/or depressed over the last 7 days?



8.2. SECTION 2

The following questions ask about changes in your life related to your VVC symptoms **since beginning this study**. Please check the box next the number that best describes your experience.

9. Since beginning this study, how would you describe the change in your overall sexual satisfaction related to your VVC?