SCYNEXIS, Inc.

Protocol No. SCY-078-204

[redacted]

STATISTICAL ANALYSIS PLAN

A Phase 2, Multicenter, Randomized, Double-Blind, Double-Dummy, Active-Controlled, Dose-Finding Study to Compare the Safety and Efficacy of Oral SCY-078 vs. Oral Fluconazole in Subjects with Acute Vulvovaginal Candidiasis **(DOVE)**

[redacted]

Version 2.0
Revision History:

[redacted]

06-Jun-2018 | 11:20:33 EDT

[redacted]

| 07:38:16 EDT

[redacted]

Table of Contents

List of Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
AUC	Area under the concentration-time curve
AVVC	Acute Vulvovaginal Candidiasis
BID	twice daily
CFR	Code of Federal Regulations
Cmax	Maximum concentration
CRF	Case Report Form
CRO	Contract Research Organization
DMP	Data Management Plan
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intention To Treat
LOCF	Last Observation Carried Forward
mITT	Modified Intention To Treat
OGD	Office of Generic Drugs
PI	Principal Investigator
PP	Per Protocol
PK	Pharmacokinetic
QD	once daily
SD	Standard Deviation
SAE	Serious Adverse Event
SAS	Statistical Analyzing System
SOP	Standard Operating Procedure
TOC	Test of cure
VSS Scale	Vulvovaginal Signs and Symptoms Scale

1. INTRODUCTION

This Statistical Analysis Plan (SAP) is based on the study Protocol Amendment 1 (Version 2.0) dated 13 Jul 2017.

This document provides additional details concerning the statistical analyses outlined in the protocol and reflects any changes to the protocol from any amendments. This plan will not repeat all the definitions given in the protocol but will provide further details of the summaries and analyses planned therein.

2. STUDY OBJECTIVES

Primary Objective:

- To identify the recommended dose of oral SCY-078 in subjects with moderate to severe Acute Vulvovaginal Candidiasis (AVVC) by comparing the efficacy of different dose levels and dosing regimens of oral SCY-078

Secondary Objectives:

- To evaluate the efficacy of oral SCY-078 in subjects with AVVC based on mycological and clinical outcomes
- To evaluate the safety and tolerability of different dose levels and dosing regimens of oral SCY-078 in subjects with AVVC

Exploratory Objectives:

- To explore the efficacy of SCY-078 in subjects with AVVC based on potassium hydroxide (KOH) testing at the TOC visit
- To explore the efficacy of SCY-078 in subjects with AVVC based on additional clinical outcomes
- To explore the prevalence of Candida species among subjects with AVVC
- To explore the in vitro activity of SCY-078 against baseline Candida spp. isolates
- To explore clinical and mycological outcomes by Candida species
- To evaluate the PK of SCY-078 after oral administration of different dose levels and dosing regimens of SCY-078 in subjects with AVVC

3. STUDY DESIGN

This is a multicenter, randomized, double-blind, double-dummy, active-controlled, dose-finding study to compare the efficacy, safety and tolerability of oral SCY-078 compared to oral

fluconazole in adult female subjects 18 years and older with moderate to severe AVVC. Approximately 180 eligible subjects (30 subjects per treatment group) will be enrolled and randomized into the study.

The primary objective of this study is to identify the recommended dose of oral SCY-078 in subjects with moderate to severe AVVC by comparing the efficacy of different dose levels and dosing regimens of SCY-078.

The study will consist of a Screening visit, a Baseline visit on Day 1, a study visit on Day 3 (which will consist of an on-site visit for PK sampling for a subset of subjects and a phone contact for all other subjects), a TOC visit (which will include PK sampling for the PK Subset of subjects) on Day 10 (±2) and a FU visit on Day 25 (+4). The Screening and Baseline visits may be combined. Efficacy, safety, tolerability and PK assessments will be conducted for the study.

At Screening, subjects who are experiencing vulvovaginal symptoms will be evaluated by the investigator, who will obtain a vaginal sample for local KOH testing and for fungal culture and species identification by the central laboratory. Susceptibility testing will be done at the central laboratory for all positive cultures for *Candida* spp. Additional vaginal samples will be collected, if clinically indicated, to be examined for the presence of other pathogens (e.g., causative agents for bacterial vaginosis, *Trichomonas*, *Herpes* virus, *N. gonorrhea*, *Chlamydia*, human papillomavirus or other mixed infections) by a qualified laboratory and for the determination of vaginal pH by the investigator. The investigators and the subjects will rate the signs (edema, erythema and excoriation) and symptoms (itching, burning and irritation) of infection, respectively, on a standardized vulvovaginal signs and symptoms scale (the Vulvovaginal Signs and Symptoms [VSS] Scale). Safety procedures, including an abbreviated physical 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 ≥7 with at least 2 signs or symptoms having a score of 2 (moderate) or greater in the VSS Scale, a positive KOH test and a normal vaginal pH (≤4.5).

At the Baseline visit (which may be combined with the Screening visit), eligible subjects will be randomized in equal allocation (at a 1:1:1:1:1:1 ratio) to one of the following 6 active treatment groups (5 experimental groups and 1 active comparator group):

- Treatment Group 1: oral SCY-078 750 mg QD on Day 1 only
- Treatment Group 2: oral SCY-078 300 mg BID on Day 1 only
- Treatment Group 3: oral SCY-078 450 mg BID on Day 1 only
- Treatment Group 4: oral SCY-078 150 mg BID on Days 1 to 3
- Treatment Group 5: oral SCY-078 300 mg BID on Days 1 to 3
- Treatment Group 6: oral fluconazole 150 mg QD on Day 1 only

Subjects will receive randomized treatment from Day 1 through Day 3. For the purpose of maintaining treatment blinding, all randomized subjects will receive matching SCY-078 placebo

tablets and/or matching fluconazole placebo capsules as needed based on treatment assignment, in a double-dummy fashion. During treatment days, subjects will rate their vulvovaginal symptoms and record dosing details, AEs and concomitant medication use daily on subject diaries. On Day 3, a PK Subset consisting of 10 subjects per treatment group (total of 60 subjects) will visit the site to have PK samples drawn pre-dose (immediately before dosing) and at 2-6 hours' post-dose of either the morning or evening dose. Day 3 will be an on-site visit for PK subjects and a phone contact visit (with a window of +3 days) for non-PK subjects. All subjects (both PK and non-PK subjects) will continue to take their assigned study treatment and rate their symptoms of infection within their subject diaries. Treatment compliance will be reviewed either on site or by phone for all subjects. Study drug may be collected from PK subjects who have completed study drug dosing at the time of this visit.

At the TOC visit (Day 10 [±2]) vaginal samples will be obtained for local KOH testing and for fungal culture by the central laboratory. In addition, susceptibility testing will be done at the central laboratory for all positive cultures for *Candida* spp. The investigators and the subjects will rate the signs and symptoms of infection, respectively, on the VSS Scale. An abbreviated physical exam, vital sign measurements and safety laboratory tests will also be performed.

Additionally, a single PK sample will be obtained at any convenient time of the day from the PK Subset only. For the PK Subset, the TOC visit must occur as close to Day 10 as possible. All subjects will return their subject diaries. Compliance with study drug dosing will be evaluated and study drug will be collected for all subjects who did not return their study drug on Day 3.

At the FU (Day 25[+4])) visit, vaginal samples will be obtained for local KOH testing and for fungal culture by the central laboratory. In addition, susceptibility testing will be done at the central laboratory for all positive cultures for *Candida* spp. The investigators and the subjects will rate the signs and symptoms of infection, respectively, on the VSS Scale to evaluate clinical outcome.

4. HARDWARE AND SOFTWARE

Statistical analysis will be performed following Novella standard operating procedures and on the Novella computer network. All statistical analysis will be performed using SAS Version 9.3 with program code prepared specifically for the project by qualified Novella statisticians and SAS programmers.

The SAS programs will generate rich-text-formatted (RTF) output with the "RTF" extension using the SAS Output Delivery System (ODS). The summary tables and listings will be formatted using the Times New Roman 9-point font. The RTF output is included in report documents prepared with Microsoft Word and converted to PDF format without typographical change.

Datasets will be created and taken as input to validated SAS programs to generate the report-ready tables, listings, and figures. Each output display will show the names of the data sets and SAS program used to produce it.

5. DATABASE CLOSURE

After completion of all data review procedures, validation of the project database, and approval of the data review document by the study sponsor, the clinical database will be closed and the study will be unblinded. Any change to the clinical database after this time will require written authorization, with explanation, by the Sponsor and the Biostatistician.

6. SAMPLE SIZE DETERMINATION

This is an exploratory study and no formal sample size calculation was performed. Approximately 180 subjects will be enrolled and randomized in an equal allocation (at a 1:1:1:1:1:1 ratio) to the six study treatment groups (see Table 1). Thirty subjects per group are estimated to be adequate to perform an initial assessment of the safety and tolerability as well as the potential efficacy of SCY-078 in subjects with AVVC.

7. ANALYSIS POPULATIONS

The following analysis sets/populations will be used in this trial:

- **Intent-to-Treat (ITT) population**: All randomized subjects
- **Modified Intent-to-Treat (mITT) Population**: All randomized subjects who have a positive KOH test and a confirmed positive mycological culture for yeast at Baseline.
- **Per Protocol (PP) population**: All mITT subjects who have completed the study drug treatment, who have a TOC evaluation AND who have no major protocol deviations (e.g., violation of Inclusion/Exclusion criteria, use of interfering concomitant medications). The TOC evaluation will be considered an evaluation within the Visit 4/ TOC/ Day 10 analysis window and may include unscheduled visits from subjects who attended the TOC visit late. Subjects to be included in the PP population will be determined by the Sponsor/CRO prior to the unblinding of the study. Prior to breaking the blind, additional criteria for exclusion from the PP population may be included to accommodate for unforeseen events that occurred during the conduct of the study.
- **Safety population**: All randomized subjects who received at least one dose of study drug and who have at least one post-Baseline evaluation
- **Pharmacokinetic (PK) population**: All randomized subjects who received study drug and provided at least one PK sample.

The mITT population will be the primary population for efficacy analysis. The ITT and PP population will be secondary for the primary and secondary endpoints only. The Safety population will be used for the analyses of safety endpoints.

All efficacy analyses will be conducted according to the randomized treatment assignment; all safety analyses will be conducted according to the treatment actually received.

8. HANDLING OF MISSING DATA

For the analyses of efficacy endpoints, subjects who have a missing value at the TOC visit or FU visit will be assigned as treatment failures, i.e., non-responders or positive mycological outcome.

The handling of below level of quantitation (BLQ) values in PK analysis will be described in the section below.

No other imputation will be used unless otherwise specified.

9. INTERIM ANALYSIS

No interim analysis is planned for this study.

10. DATA CONVENTIONS FOR ANALYSIS

10.1 General Statistical Principles

All statistical tests will be performed at the unadjusted 0.05 (two-sided) or equivalently 0.025 (one-sided) level of significance. The study is not powered for formal statistical comparisons.

All observed and derived variables (e.g., change from baseline, response status) used in the summaries of analyses will be presented in by-subject listings. Descriptive statistics will be used to provide an overview of the efficacy and safety results. For categorical parameters, the number and percentage of subjects in each category will be presented. The denominator for percentage will be based on the number of subjects appropriate for the purpose of analysis. For continuous parameters, descriptive statistics will include number of subjects, mean, standard deviation (SD), median, minimum, and maximum.

10.2 Study Day

Day 1 is defined as the date of first study drug administration. Study day is calculated relative to the date of Day 1.

10.3 Baseline and Change from Baseline

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.

10.4 Analysis Visit Window

Wherever applicable, efficacy and safety endpoints at Visit 1/ Screening, Visit 2/ Baseline, Visit 3/ Day 3, and Visit 5/ FU/ Day 25 will be analyzed according to their nominal visits . Visit 4/ TOC/ Day 10 will be analyzed according to the analysis window of study day 8 to study day 13, inclusive. Unscheduled visits from subjects who attended the TOC visit late will be included if within the analysis window. The bounds may be revised after reviewing blinded data. If more than one evaluation is assigned to this window, the evaluation closed to study day 10 will be used for the analysis. If the two visits are equidistant from the target day, the earlier visit will be used. Unscheduled visit assessments will be displayed in by-subject listings, without being included in the summaries.

11. STATISTICAL EVALUATION

11.1 Subject Disposition

The number and percentage of subjects screened, randomized, included in each analysis population, completing the study, withdrawing from the study (together with the reasons for withdrawal) will be summarized using frequencies and percentages by treatment group. A by-subject listing will be presented for all subject enrollment and disposition. Screen failures and subjects not randomized will be presented in by-subject listings.

The number of days in the study (date of study completion / discontinuation minus date of Day 1 plus 1) will be summarized using descriptive statistics for each treatment group.

Tabulation by study site will be provided.

11.2 Protocol Deviation

Protocol deviations will be logged into the IL2 database and displayed in a by-subject listing. One exception to this is Out of Window (OOW) Visit protocol deviations. A report from DSG eCaseLink will be run at the end of the study to obtain a listing of all OOW Visit protocol deviations.

11.3 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized overall and by treatment for the ITT, PP and Safety populations. The following demographic and baseline variables will be included:

- Age (years)
- Race
- Ethnicity
- Weight (kg)
- Height (cm)
- Body mass index (kg/m2)

11.4 Study Medication and Visit Compliance

For the purpose of blinding, the number and appearance of dosage units will be the same across all treatment groups, as follows:

- Day 1: 5 tablets for the morning dose + 3 tablets and 1 capsule for the evening dose
- Day 2 and Day 3: 2 tablets for the morning dose + 2 tablets for the evening dose

The following parameters of study drug exposure and compliance will be summarized for each treatment group:

- Total number of doses taken, calculated as 6 minus total number of doses missed; if a subject's drug accountability missing, the subject's number of doses taken will be assumed as missing
- Total number of bottles returned
- Total number of tablets/capsules taken, calculated as total number of tablets/capsules dispensed minus total number of tablets/capsules returned; total number of tablets/capsules = 17 (9 on Day 1 plus 4 on Day 2 and Day 3 each)
- Subjects with any non-compliance issue based on investigator's review of subject diary

11.5 Prior and Concomitant Medications

Prior (within the previous 28 days and with stop dates prior to first dose of study drug) and concomitant (ongoing or with stop dates on or after first dose of study drug) medications will be presented for the safety population in a by-subject listing for each treatment group. If the medication is ongoing or the stop year is missing, the medication will be considered as received for the entire duration of the study. Medications will be coded using WHO-DD terminology.

For the determination of prior vs concomitant medications, the following rules regarding the stop date will be applied:

- If only year was recorded, and it is before Baseline, it is a prior medication; if year is same or after Baseline, it is assumed to be a concomitant medication.
- If day is missing, but month and year are before Baseline, it is a prior medication; if month and year are the same as Baseline, it is assumed to be a concomitant medication; if month and year are after Baseline, it is a concomitant medication.
- If start date is after Baseline, it is a concomitant medication regardless.

In addition, prior and concomitant medications will be summarized by treatment, WHO-DD Anatomical-Therapeutic-Chemical (ATC) classification and preferred term (PT).

11.6 Medical History and Concurrent Procedures

Medical history (including previous and ongoing medical conditions) will be coded using MedDRA and presented in a by-subject listing.

11.7 Physical Examination

Abnormal findings of physical examination at Screening and TOC will be presented in a by-subject listing.

11.8 Efficacy Endpoints

11.8.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the percentage of subjects with Clinical Cure at the TOC visit.

Clinical Cure is defined as complete resolution of signs and symptoms of vulvovaginal infection without need for further antifungal treatment. Specifically, for complete resolution, any sign or symptom should be absent (score = 0) by the TOC visit. If any sign or symptom is missing, the subject's Clinical Cure status will be considered as missing.

Conversely, Clinical Failure is defined as no response to therapy or incomplete resolution of signs and symptoms or need for additional vulvovaginal or systemic antifungal therapy. If the subject receives or self-administers topical drug therapy for the treatment of vulvovaginal irritation/pruritus such as topical analgesic or corticosteroid after completing treatment with the study drug and before the TOC visit, the subject is considered a clinical failure.

The signs (edema, erythema and excoriation or fissures) and symptoms (itching, burning and irritation) of infection will be assessed by the investigator and the subject, respectively, on the VSS Scale. The VSS Scale is a standardized, predefined scale where each sign and symptom will

be given a numerical rating based on severity (absent = 0; mild = 1; moderate = 2; severe = 3) to calculate a total composite score.

11.8.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints include the following:

- The percentage of subjects with Mycological Eradication (negative fungal culture) at the TOC and FU visit.

  Mycological Eradication is defined as a subject with negative culture (no growth) for *Candida* species. Conversely, Mycological Persistence is defined as a subject with positive culture for *Candida* species.

- The percentage of subjects with both Clinical Cure and Mycological Eradication at the TOC visit. If either component assessment is missing, the subject will be considered as missing for this endpoint and imputed as non-responders in the analysis
- The percentage of subjects with both absence of signs and symptoms and Mycological Eradication at the FU visit. If either component assessment is missing, the subject will be considered as missing for this endpoint and imputed as non-responders in the analysis
- The percentage of subjects with Continued Clinical Response at the Follow-up (FU) visit, defined as continued absence of signs and symptoms in subjects who achieved Clinical Cure at the TOC visit
- The time to resolution of signs and symptoms after initiation of study drug, defined as time (days) from first dose of study medication to the first resolution of signs and symptoms. Subjects who discontinued early will be censored at the last available assessment.

11.8.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints include the following:

- Percentage of subjects with a negative KOH test at the TOC visit
- Percentage of subjects who are free of signs and symptoms at the FU visit
- Percentage of subjects by *Candida* species infection at Baseline
- Percentage of isolates susceptible to SCY-078 and fluconazole at the TOC and FU visits
- Percentage of subjects with clinical cure at TOC by *Candida* species at Baseline
- Percentage of subjects with mycological eradication at TOC by *Candida* species at Baseline

11.9 Efficacy Analyses

11.9.1 Primary Efficacy Analysis

The primary efficacy analysis will be conducted using the mITT (primary analysis population), ITT and PP populations.

The primary endpoint (clinical cure at TOC) will be analyzed using a Cochran-Mantel-Haenszel row mean scores test stratified by site. Pairwise treatment comparisons of SCY-078 vs. active comparator (fluconazole) will be performed using a Fisher's Exact test; p-values and 95% confidence intervals for odds ratio will be presented. Subjects whose results are missing at Day 10 (TOC) will be imputed as failures in the analysis. A sensitivity analysis will be performed where subjects with missing values will be removed from the analysis.

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 comparisons of SCY-078 vs. fluconazole; p-values and 95% confidence intervals will be presented for the differences between treatment groups.

11.9.2 Secondary Efficacy Analyses

The secondary efficacy analyses will be conducted using the mITT, ITT and PP populations.

Binary efficacy endpoints (mycological eradication, composite clinical cure and mycological eradiation, and continued clinical response at FU) will be analyzed using the same methods/tests as described for the primary efficacy endpoint.

Time to resolution of signs and symptoms after initiation of study drug will be analyzed using Kaplan-Meier methods. Pairwise treatment comparisons of SCY-078 vs. fluconazole will be performed using log-rank test.

11.9.3 Exploratory Efficacy Analyses

The exploratory efficacy analyses will be conducted using the mITT and PP populations, following the same methods/tests as described for the primary and secondary endpoints.

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.

11.10 Safety Analysis

Safety summaries will be performed on the Safety population.

11.10.1 Adverse Events

AE terms will be coded using MedDRA dictionary. A treatment-emergent AE (TEAE) is defined as an AE that starts or worsen on or after the date of the first dose of study medication. If relationship to treatment is missing, the event will be conservatively considered as being related to study drug. If severity is missing, a separate category of missing severity will be included in the summary table, and no imputation of severity will be performed. Through the data cleaning process, all attempts will be made to avoid missing values for relationship and severity.

All AEs will be presented in a by-treatment and by-subject listing, detailing the verbatim term given by the investigator, the preferred term (PT), system organ class (SOC), onset date, end date, severity, outcome, relationship to study drug, action taken with study drug, other action taken, seriousness and criteria for seriousness. Serious AEs (SAEs) and TEAEs leading to study discontinuation will also be presented in a separate listing.

An overall summary of AEs will be presented by treatment and overall. The summary will include the total number of events, frequency counts and percentages with:

- Any AE
- Any TEAE
- Any serious TEAE
- Any treatment-related TEAE, including definitely related, probably related, and possibly related
- Any TEAE leading to study drug discontinuation

Summaries of the incidence of TEAEs will be displayed by treatment according to the following:

- All TEAEs by SOC in alphabetical order and PT in descending order of frequency (the combined frequency in the two active treatments)
- All TEAEs by SOC, PT, and maximum severity (mild, moderate, or severe)
- All TEAEs by SOC, PT, and maximum causality (not related, related) to the study drug

At each level of summarization, a subject will be counted once if he/she reported one or more events. The severity of TEAEs and relationship to study drug will be summarized in a similar manner. For summaries of relationship to study drug, a subject will be classified according to the closest relationship. For summaries of TEAE severity, a subject will be classified according to the highest severity.

11.10.2 Clinical Laboratory Testing

Absolute values and changes from baseline will be summarized for clinical laboratory (chemistry and hematology) results using descriptive statistics. Shift tables for each clinical laboratory test will cross-tabulate the number of subjects with values below the laboratory reference range (low), values within the laboratory reference range (normal) or above the laboratory range (high)

at baseline with the number of subjects with low, normal or high values at each post-baseline time point. Normal ranges and values outside the normal ranges will be identified by the central laboratory. A separate listing of out of normal range laboratory results will be provided.

Urine pregnancy test will be presented with subject childbearing potential in a by-subject listing.

11.10.3 Vital Signs

Vital signs including blood pressure (systolic and diastolic), heart rate, respiratory rate and body temperature will be presented in a by-subject listing by visit. Absolute values and change from baseline value will be summarized by treatment group using descriptive statistics.

11.11 Pharmacokinetics

For subjects that consent to providing PK samples, blood will be drawn at the Day 3 and TOC (Day 10) visits. On Day 3, samples will be collected pre-dose (immediately before dosing) and at 2-6 hours post-dose of either the morning or evening dose (5^{th} or 6^{th} dose of study drug). On Day 10, a single PK sample will be collected at any time. For the PK Subset, the TOC visit must occur as close to Day 10 as possible.

The analyses of PK concentrations and PK parameters will be described in a separate report. The report will be prepared by a vendor selected by Scynexis after database lock.

12. CHANGES FROM THE PROTOCOL AND PLANNED ANALYSES

This SAP reflects the analysis plan outlined in the study protocol without significant change. Any analysis changes or additional analysis not specified in this SAP will have the status of unblinded and exploratory investigations.

13. HEADINGS

Each page of the analysis will show the sponsor's name, the investigational product, and the protocol number. Report tables will be embedded in the MS Word report document from SAS program output without change. The footer of each table will show the name of the SAS program module which generated it, the names of all data sets providing input data in the program and the date and time the table was generated.

14. ARCHIVING AND RETENTION OF DOCUMENTS

After finalization of the analysis, the following will be archived at Novella Clinical and/or with the study sponsor:

- SAP and any amendments

- All SAS code used in the project for statistical analysis, report tables generation, and analysis data set creation
- Tables, listings and figures as included in the clinical study report
- SAS study data tabulation model (SDTM) and analysis dataset model (ADaM) datasets

15. OUTLINE OF PROPOSED TABLES, LISTINGS AND FIGURES