PRS COVER PAGE for STATISTICAL ANALYSIS PLAN

TITLE: A Phase 3, Randomized, Double-Blind Study to Evaluate the Efficacy and Safety of VT-1161 Oral Capsules versus Fluconazole and Placebo in the Treatment of Acute Vulvovaginal Candidiasis Episodes in Subjects with Recurrent Vulvovaginal Candidiasis (VMT-VT-1161-CL-017)

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STATISTICAL ANALYSIS PLAN

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CONFIDENTIAL AND PROPRIETARY INFORMATION

STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

This Statistical Analysis Plan has been prepared in accordance with team reviewers' specifications.

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1. INTRODUCTION

This document describes the statistical methods and data presentations to be used in the summary and planned analysis of data from Protocol VMT-VT-1161-CL-017. Background information is provided for the overall study design and objectives. The reader is referred to the study protocol, case report forms (CRFs) and randomization specification form for details of study conduct and data collection.

1.1. STUDY OVERVIEW

This is a Phase 3, multi-center, randomized, double-blind, placebo-controlled, parallel-group study. The study will evaluate the efficacy and safety of oral VT-1161 capsules versus fluconazole in the treatment of acute vulvovaginal candidiasis episodes in subjects with recurrent vulvovaginal candidiasis (RVVC). In addition, the study will evaluate the efficacy of oral VT-1161 compared to placebo in the prevention of RVVC. The study consists of two phases: 1) an Induction Phase for the treatment of the acute vulvovaginal candidiasis (VVC) episode in which subjects will be randomly assigned in a 2:1 ratio (VT-1161 to fluconazole) to receive either a) a 600 mg VT-1161 dose on Day 1 and 450 mg VT-1161 dose on Day 2, or b) 3 sequential 150 mg oral doses (every 72 hours) of over-encapsulated fluconazole, and 2) a Maintenance phase in which subjects randomized to receive VT-1161 in the Induction Phase will receive 150 mg VT-1161 weekly for 11 weeks and subjects initially randomized to over-encapsulated fluconazole in the Induction Phase will received placebo weekly for 11 weeks. The maintenance phase will include follow-up for each subject through Week 50.

Once subjects have provided informed consent or assent (for those ages 12-17), the investigational site will evaluate all subjects by completing a review of pertinent medical history, obtaining vital signs, height and weight, electrocardiogram (ECG) and laboratory tests, reviewing clinical signs and symptoms of vulvovaginitis, performing a complete physical examination including speculum examination of the vagina, performing a potassium hydroxide (KOH) wet mount test from a vaginal smear to confirm the presence of yeast, and collecting vaginal swabs to establish a baseline culture for identification of fungal species. Eligible subjects must have an acute VVC episode at Screening, defined as a total signs and symptoms score of $\geq$3 and a positive local KOH wet mount preparation from a vaginal smear revealing filamentous hyphae/pseudohyphae and/or budding yeast cells and must meet other initial entry criteria.

Once eligibility is confirmed, subjects will be randomized in a 2:1 ratio (VT-1161: fluconazole) to enter the Induction Phase. During the Induction Phase, the presenting acute VVC episode will be treated with either 600 mg VT-1161 (4 x 150 mg capsules) on Day 1 and 450 mg VT-1161 (3 x 150 mg capsules) on Day 2, or 3 sequential 150 mg oral doses (every 72 hours) of over-encapsulated fluconazole. Subjects will return approximately 14 days after the first dose of VT-1161 or over-encapsulated fluconazole to determine if the acute VVC episode has resolved (defined by a signs and symptoms score of <3). If the acute VVC has not resolved, the subject will be considered an Induction Failure and encouraged to see their physician for follow-up. All subjects in which the acute VVC infection has resolved will continue into a Maintenance Phase. Day 1 (Screening) is defined as the first day of investigational medicinal product (IMP) administration and subsequent study days are defined by the number of consecutive days thereafter. Day 14 is defined as the first day of weekly dosing of IMP administration.

Vulvovaginal signs and symptoms will be evaluated at Screening and at each subsequent study visit. A local mycological assessment using KOH wet mount followed by microscopy will be performed at Screening to determine study eligibility and at any study visit where a recurrent acute VVC episode is suspected. In addition, from the collected vaginal swabs, culture growth will be evaluated by the central mycology laboratory. Blood samples for assay of VT-1161 plasma concentrations will be collected from subjects at Day 14, Weeks 14 and 50. Intense sampling will be obtained from approximately 12 consenting subjects at participating sites on Day 1 and on Day 2, at time points predose and 1, 2, 4, and 8 hours after dosing. Subject safety will be monitored by the reporting of adverse events (AEs) and changes in vital signs, physical and vaginal exam parameters, ECGs, and safety laboratory parameters, including pregnancy tests for women of child-bearing potential.

1.2. GLOSSARY OF ABBREVIATIONS

AE	adverse event
ANCOVA	analysis of covariance
BMI	body mass index
CI	confidence interval
CRF	case report form
ECG	electrocardiogram
IMP	investigational medicinal product
ITT	intent-to-treat
IWRS	interactive web response system
KOH	potassium hydroxide
LS	least squares
mITT	modified intent to treat
PK	pharmacokinetic
PP	per-protocol
QTcF	Fridericia-corrected QT interval
SAE	serious adverse event
TEAEs	treatment-emergent adverse events
VT-1161	IMP, oral inhibitor of fungal CYP51
RVVC	recurrent vulvovaginal candidiasis
VVC	vulvovaginal candidiasis

2. OBJECTIVES

Primary:

- To evaluate the efficacy of oral VT-1161 in the prevention of culture-verified acute episodes of VVC through Week 50 in RVVC subjects.
- To compare the efficacy of oral VT-1161 and fluconazole in the treatment of an acute episode in RVVC subjects.

Secondary:

- To evaluate the safety and tolerability of oral VT-1161 through Week 50.

3. GENERAL STATISTICAL CONSIDERATIONS

3.1. PRIMARY STUDY HYPOTHESES

The primary null hypothesis for this study is that the proportion of subjects with one or more culture-verified acute VVC episodes post randomization through Week 50, which includes

subjects with an unresolved VVC episode during the Induction Phase (post-randomization through Day 14), is the same for subjects treated with VT-1161 and those treated with placebo. The alternative hypothesis is that the proportion of subjects with one or more culture-verified acute VVC episodes post randomization through Week 50, which includes subjects with an unresolved VVC episode during the Induction Phase (post-randomization through Day 14), is different for subjects treated with VT-1161 and those treated with placebo. A culture-verified acute VVC episode during the Maintenance phase (considered a recurrent episode) is defined as a positive culture for Candida species associated with clinical signs and symptoms score of ≥3.

The key secondary null hypothesis for this study is that the proportion of subjects whose acute VVC has resolved by Day 14 is inferior (i.e. less) for subjects treated with VT-1161 compared to those treated with fluconazole. The alternative hypothesis is that the proportion of subjects whose acute VVC has resolved by Day 14 is non-inferior for subjects treated with VT-1161 compared to those treated with fluconazole. A non-inferiority margin of 15% will be used for the testing of this hypothesis.

3.2. SAMPLE SIZE

The study will enroll approximately180 total subjects (120 in the VT-1161 arm and 60 in the fluconazole/placebo arm). For the primary efficacy endpoint determination, a sample size of 82 active subjects and 41 fluconazole/placebo subjects provides at least 90% power to detect a treatment difference between the VT-1161 treatment group and the fluconazole/placebo treatment group in the percentage of subjects with one or more culture-verified acute VVC episodes during the Maintenance Phase (post randomization through Week 50). (PASS 2008: Fisher's exact test, two-sided alpha=0.05, and assuming 50% of fluconazole/placebo subjects have recurrence). For the first key secondary endpoint, the proportion of subjects with resolved acute VVC infections (clinical signs and symptoms score of <3) at Day 14 following treatment with VT-1161 or fluconazole, a sample size of 120 subjects in the VT-1161 arm and 60 subjects in the fluconazole/placebo arm provides at least 88% power to detect non-inferiority between the VT-1161 treatment group and the fluconazole treatment group with a non-inferiority margin of 15% and a type 1 error rate of 0.05. (PASS 2008: Z-test for two independent proportions, one-sided alpha = 0.025, non-inferiority margin = 15%, and assuming that 90% of fluconazole subjects resolve their acute VVC infection).

For the primary endpoint, the placebo rate was based on data generated in the Phase 2b RVVC study; the primary efficacy outcome measure in this study was the proportion of subjects with one or more culture verified acute VVC episodes during the Maintenance Phase through Week 48 of the study in the ITT population (all randomized subjects). Culture-verified acute VVC was defined as a positive fungal culture for Candida species associated with a total signs and symptoms score of ≥ 3. The proportion of subjects with one or more culture-verified acute VVC episodes through Week 48 was lower in the VT-1161 dosing regimens (0-7%) compared with the placebo group (52.2%). This difference was statistically significant in all VT-1161 treatment groups compared with placebo ($p<0.0001$). When powering the VMT-VT-1161-CL-017 study, it was determined that a separation of at least 35% between the treatment groups would be a clinically meaningful separation. Thus, the sample size was powered to detect at least a 35% separation between the treatment groups.

Treatment of RVVC Non-inferiority justification

Fluconazole Assumptions

The Fluconazole clinical improvement (signs and symptoms < 2) rate at Day 14 was calculated using the data recently collected from the induction period of the following Mycovia studies:

- VMT-VT-1161-CL-006, titled 'A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Efficacy and Safety of VT-1161 Oral Tablets in the Treatment of Patients With Recurrent Vulvovaginal Candidiasis'.
- VMT-VT-1161-CL-011, titled 'A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of VT-1161 Oral Capsules in the Treatment of Subjects with Recurrent Vulvovaginal Candidiasis'
- VMT-VT-1161-CL-012, titled 'A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of VT-1161 Oral Capsules in the Treatment of Subjects with Recurrent Vulvovaginal Candidiasis'

Mycovia study CL-006 enrolled 215 subjects who received fluconazole to clear an acute VVC infection. At Day 14, 84.7% of subjects had clinical improvement (signs and symptoms of 0 or 1). Mycovia's 2 pivotal Phase 3 studies (CL-011 and CL-012) have clinical improvement rates of 78.1% (374 subjects) and 80.1% (366 subjects) at Day 14. When combining the data from Phase 2b and the 2 Phase 3 studies, the clinical improvement rate in 955 subjects at Day 14 is 80.3%.

Placebo Assumptions

The placebo clinical improvement rate was calculated using the results from the Scynexis Second Quarter 2020 Financial Results and Company Updates (https://www.globenewswire.com/news-release/2020/08/10/2075630/0/en/SCYNEXIS-Reports-Second-Quarter-2020-Financial-Results-and-Provides-Company-Update.html). Scynexis reported topline results from 2 of their pivotal Phase 3 studies in subjects with acute VVC:

- VANISH-306, titled '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 Candidasis.'
- VANISH-303, titled '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 Candidasis.'

VANISH-306 with 84 placebo patients had clinical improvement of 54.8% at Day 10 and VANISH-303 with 98 patients had clinical improvement of 36.7% at Day 10. The projected clinical improvement rates at Day 14, are 57.0% and 41.0%. The projected rates for Day 14 were determined for each study by using the formulas for the clinical improvement lines in each study (VANISH-306: $y = 0.56x + 49.2$, VANISH-303: $y = 1.087x + 25.83$). For each study, to determine the formula for the line for clinical improvement, the slope was derived using the Day 10 and Day 25 clinical cure rates. Mycovia is assuming the slope between Day 10 and Day 25 for clinical improvement for each study is the same as the slope between Day 10 and Day 25 for clinical cure for each study. A weighted average of the Day 14 projected rates from the 2 Phase 3 studies was used as the expected placebo clinical improvement rate of 48.4%.

NI Margin Justification
Fluconazole has a clinical improvement (signs and symptoms < 2) rate of 80.3% at Day 14. Placebo has a clinical improvement rate of 48.4% at Day 14. Thus, an estimate of the effect of fluconazole to treat an acute VVC infection versus no intervention in subjects with RVVC is 31.9%. Per the FDA guidance document on Non-Inferiority Clinical Trials to Establish Effectiveness, a non-inferiority margin that is at most half the effect of the control drug should be used. A non-inferiority margin of 15% was selected for this trial which is less than 50% of the effect of the control drug. The placebo rate in the NI margin calculation is a conservative estimate of the placebo improvement rate in RVVC subjects since the placebo rate is from VVC subjects. This is a conservative estimate for the placebo improvement rate in RVVC subjects as it has been shown to be harder for subjects with RVVC to clear their infections. Per the package insert for Fluconazole (https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f694c617-3383-416c-91b6-b94fda371204), for all endpoints that are in the insert (clinical cure, mycologic eradication, and therapeutic cure), the rates were lower in RVVC subjects than in VVC subjects. Thus, the true effect of fluconazole over placebo is likely greater than 31.9%.

Treatment of Acute VVC Non-inferiority justification

Fluconazole Assumptions
The Mycovia Fluconazole clinical cure rate (clinical signs and symptoms score of 0) in RVVC was determined by first using the data from the induction period of the following Mycovia studies:

- VMT-VT-1161-CL-006, titled 'A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Efficacy and Safety of VT-1161 Oral Tablets in the Treatment of Patients With Recurrent Vulvovaginal Candidiasis'.
- VMT-VT-1161-CL-011, titled 'A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of VT-1161 Oral Capsules in the Treatment of Subjects with Recurrent Vulvovaginal Candidiasis'
- VMT-VT-1161-CL-012, titled 'A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of VT-1161 Oral Capsules in the Treatment of Subjects with Recurrent Vulvovaginal Candidiasis'

Mycovia study CL-006 enrolled 215 subjects who received fluconazole to clear an acute VVC infection. At Day 14, 59.5% of subjects had clinical cure (signs and symptoms of 0). Mycovia's 2 pivotal Phase 3 studies (CL-011 and CL-012) have clinical cure rates of 58.3% (374 subjects) and 55.2% (366 subjects) at Day 14. When combining the data from Phase 2b and the 2 Phase 3 studies, the clinical improvement rate in 955 subjects is 57.4%. The package insert for fluconazole notes a 57% clinical cure rate in RVVC patients and an 80% clinical cure rate in patients with acute VVC. The rate observed in the 3 Mycovia studies is numerically the same as the package insert (57.4% vs 57%). Thus, the clinical cure rate of 80% for subjects with acute VVC will be used in the NI calculation to determine the benefit of fluconazole over no intervention.

Placebo Assumptions
The placebo clinical cure rate was calculated using the results from the Scynexis Second Quarter 2020 Financial Results and Company Updates (https://www.globenewswire.com/news-release/2020/08/10/2075630/0/en/SCYNEXIS-Reports-Second-Quarter-2020-Financial-Results-

and-Provides-Company-Update.html). Scynexis reported topline results from 2 of their pivotal Phase 3 studies in subjects with an acute VVC infection:

- VANISH-306, titled '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 Candidasis.'
- VANISH-303, titled '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 Candidasis.'

VANISH-306 with 84 placebo patients had clinical cure of 44% at Day 10 and VANISH-303 with 98 patients had clinical cure of 28.6% at Day 10. The projected clinical cure rates at Day 14 are 46.24% and 32.95%. The projected rates for Day 14 were determined for each study by utilizing the formulas for the clinical cure lines in each study (VANISH-306: $y = 0.56x + 38.4$, VANISH-303: $y = 1.087x + 17.73$). For each study, the Day 10 and Day 25 clinical cure rates were used to determine the formula for the line for clinical cure. A weighted average of the Day 14 projected rates from the 2 studies was used as the expected placebo clinical cure rate of 39.1%.

NI Margin Justification
Fluconazole has a clinical cure (signs and symptoms = 0) rate of 80% at Day 14 in subjects with acute VVC. Placebo has a clinical cure rate of 39.1% at Day 14 in subjects with acute VVC. Thus, the effect of fluconazole to treat an acute VVC infection versus no intervention in subjects with acute VVC is 40.9%. The effect of fluconazole to treat an acute infection versus no intervention in subjects with RVVC is expected to be the same as the effect in subjects with acute VVC. A non-inferiority margin of 15% was selected for this comparison which is less than 50% of the effect of the control drug.

3.3. RANDOMIZATION AND BLINDING

A total of approximately 180 eligible subjects will be randomized in a 2:1 ratio to either VT-1161 or fluconazole/placebo based on the randomization list which will be prepared according to appropriate standard operating procedures. Randomization to treatment will be sequentially assigned to eligible subjects at the Day 1 (Screening) Visit.

This is a double-blind study. Therefore, the subjects, study investigators and their staff, all clinical staff members within Mycovia, Clinical Study Monitors, and the Study Medical Monitor will remain blinded to individual treatment assignments until the completion of the study. The only study personnel who will be unblinded to the treatments will be the Unblinded Statistician responsible for creating the final randomization list, the interactive web response system (IWRS) personnel responsible for loading the final randomization list into the IWRS system, clinical supply management (Vendor/Mycovia) and distribution personnel and bioanalytical personnel.

Should the Investigator or the Study Medical Monitor need to reveal a given subject's treatment assignment, such as in the case of a serious adverse event (SAE) report where knowledge of the IMP treatment assignment may be needed to treat the subject with the SAE, the IWRS may be accessed to break the study blind for that subject. The Investigator must contact and discuss with Mycovia's Medical Monitor the circumstances leading to his/her decision to break the blind.

3.4. HANDLING OF DATA

3.4.1. Strata and Covariates

There are no planned strata or covariates for the primary and secondary endpoints. [redacted]

3.4.2. Examination of Subject Subsets

The primary efficacy and key secondary efficacy endpoints will be analyzed by age group (12-17, 18-33, 34 and older), race (White, Black, Other), and ethnicity (Hispanic or Latino, Not Hispanic or Latino). In addition, the primary efficacy endpoint will be analyzed for subjects with a signs and symptoms score of 0, 1, or 2 at Day 14.

3.4.3. Multiple Testing and Comparisons

The primary endpoint is the proportion of subjects with one or more culture-verified acute VVC episodes (post randomization through Week 50) in the intent-to-treat (ITT) population, which includes subjects with an unresolved VVC episode during the Induction Phase (post-randomization through Day 14).

If the comparison for the primary endpoint is significant (two-sided p-value <0.05), then testing will continue for the key secondary endpoints. To control for the type I error rate at 0.05 for multiple secondary endpoints, the hierarchical/gate-keeping method will be used. Each key secondary endpoint will be tested according to the hierarchy below. For the first secondary endpoint, if VT-1161 is non-inferior to fluconazole based on the 95% confidence interval then testing will continue for the remaining key secondary endpoints. [redacted]

Hierarchy of key secondary efficacy endpoints:

- The proportion of subjects with resolved acute VVC infections (clinical signs and symptoms score of <3) at Day 14 following treatment with VT-1161 or fluconazole.
- The proportion of subjects with at least one culture-verified acute VVC episode with signs and symptoms ≥3 during the Maintenance Phase (post Day 14 through Week 50).
- Time to first recurrence of a culture-verified acute VVC episode with signs and symptoms score ≥3 during the Maintenance Phase (post Day 14 through Week 50).
- The proportion of subjects with at least one positive culture for Candida species during the Maintenance Phase.

[redacted]

3.4.4. Missing Data and Outliers

Every effort will be made to obtain required data at each scheduled evaluation from all subjects who have been randomized, including those who discontinue the study prior to the end-of-study Week 50 visit.

For scheduled visits where the investigator's assessment of clinical signs and symptoms or the culture result is missing, missing values will be imputed using the method of multiple imputation. For subjects who discontinue the study early and have missing assessments for all visits after discontinuation, the missing values for the expected scheduled visits will be imputed using the method of multiple imputation. The missing values will be imputed using the following auxiliary information: region, treatment, baseline body mass index (BMI), baseline age, ethnicity, and visit. Region, treatment, baseline BMI, baseline age, ethnicity, and visit are included as auxiliary information because it is believed that subjects with similar values for each of these parameters would respond similarly. One of the benefits of using multiple imputation is that it uses a set of values rather than a single value which better accounts for the uncertainty about the values being imputed. The procedure PROC MI in SAS will be used to generate 10 possible imputed datasets. Using these multiple imputation datasets, determination of meeting the primary endpoint of a culture-verified acute VVC episode during the Maintenance Phase will be derived. Subjects with a culture-verified acute VVC episode at any point from post Day 14 through Week 50 (including unscheduled visits) and subjects with an unresolved VVC episode during the Induction Phase (post-randomization through Day 14) will be counted as having an episode when calculating the primary endpoint. The multiple datasets containing the primary endpoint will be analyzed using a Chi-square test and the results will be combined using PROC MIANALYZE to obtain an inferential result. Here is a summary of the steps that will be performed:

1. For subjects with a missing value for clinical signs and symptoms or a missing value for culture result at a scheduled visit, who have an unscheduled visit (within the visit window) with non-missing values as outlined in Section 3.4.8, their values from the unscheduled visit will be used to replace scheduled visit values.
2. Any missing values for clinical signs and symptoms or culture result for scheduled visits will be imputed using PROC MI. Any unscheduled visit values that are not used to replace scheduled visit values, as described in Step 1, will not be used in the imputation process. The seed for the imputation procedure will be randomly generated and documented in the study files. This will result in 10 complete datasets.
3. The primary efficacy endpoint of culture-verified acute VVC episode will be derived using values from all scheduled visits from the complete datasets and all unscheduled visits that were not already used in Step 1. In other words, if an unscheduled visit for a subject is already being used to replace a missing visit in Step 1, then it would not be used again as an unscheduled visit when calculating the primary endpoint. This will result in 10 datasets with one record per person for the primary endpoint.
4. The primary efficacy endpoint will be analyzed 10 times using a Chi-square test as outlined in Section 5.2.1. The Wilson-Hilferty transformation will be applied to the Chi-square test statistics prior to combining the results using PROC MIANALYZE.
5. The results from the analysis from the 10 datasets will be combined using PROC MIANALYZE to produce an inferential result comparing the treatment groups.

The following sensitivity analyses will be performed for the primary endpoint to assess the impact of missing/censored data on the results:

1. The first sensitivity analysis will use Kaplan-Meier methods to estimate the proportion of subjects with one or more culture-verified acute VVC episodes post randomization through

Week 50. The Kaplan-Meier estimate, and 95% confidence interval will be determined and compared to the primary result. For this analysis, time to event and censoring will be calculated using the following rules:

a. Subjects who experience a culture-verified acute VVC episode post randomization through Week 50 will have their time to event calculated as the time in weeks from post randomization to the first culture-verified acute VVC episode.

b. Subjects who discontinue the study for any reason prior to Week 50 without experiencing a culture-verified acute VVC episode will be censored at the last nominal visit for which they have signs and symptoms and culture data.

c. Subjects who have missing data at any point prior to Week 50, who do not experience a culture-verified acute VVC episode and have both non-missing signs and symptoms data at Week 50 and non-missing culture data at Week 50 will be censored at the Week 50 visit.

2. Like the first sensitivity analysis, the second sensitivity analysis will also use Kaplan-Meier methods to estimate the proportion of subjects with one or more culture-verified acute VVC episodes post randomization through Week 50. The Kaplan-Meier estimate, and 95% confidence interval will be determined and compared to the primary result. For this analysis, time to event and censoring will be calculated using the following rules:

   a. Subjects who experience a culture-verified acute VVC episode post randomization through Week 50 will have their time to event calculated as the time in weeks from post randomization to the first culture-verified acute VVC episode.

   b. Subjects who discontinue the study for any reason prior to Week 50 and have no nominal visits with missing signs and symptoms or culture data prior to discontinuation will be censored at the last nominal visit prior to discontinuation for which they have signs and symptoms and culture data.

   c. Subjects who do not experience a culture-verified acute VVC episode post randomization through Week 50 with missing signs and symptoms or culture data at any point not due to COVID-19 will be censored at the last nominal visit before the first visit with missing signs and symptoms and culture data not due to COVID-19. Subjects who reach Week 50 without a culture-verified acute VVC episode and without any missing data, not due to COVID-19, will be censored at Week 50. Subjects who do not experience a culture-verified acute VVC episode post randomization through Week 50 with the only missing signs and symptoms or culture data due to COVID-19 will be censored at the last nominal visit for which they have signs and symptoms and culture data.

3. Subjects who were censored for the second sensitivity analysis due to early discontinuation or missing data not due to COVID-19 will be counted as failures. In other words, these subjects will be counted as having an episode. The proportion of subjects with episodes will be calculated and presented along with the 95% confidence intervals. The p-value from a Chi-square test comparing the 2 treatments will also be presented. The denominator for the calculation of the proportion of subjects with at least one culture-verified acute VVC episode will be the ITT population.

4. A completer analysis will be performed where subjects who did not have a culture-verified acute VVC episode and have either missing assessments for a given visit or who discontinued from the study prior to Week 50 are excluded from the analysis. The proportion of subjects with episodes will be calculated and presented along with the 95% confidence intervals. The p-value from a Chi-square test comparing the 2 treatments will also be presented.
5. The primary analysis method will be used to analyze a modified definition of the primary endpoint where subjects are included as having an acute VVC episode if 1) they meet the primary endpoint definition or 2) they have a recurrence in the absence of Investigator confirmed signs and symptoms and/or culture confirmation but took a medication known to treat VVC during the Maintenance Phase. The p-value from a Chi-square test comparing the 2 treatments will also be presented.

Sensitivity analyses will also be performed for the key secondary endpoints to assess the impact of censored data on the results.

Endpoint = proportion of subjects with resolved acute VVC infections (clinical signs and symptoms score of < 3) at Day 14 following treatment with VT-1161 or fluconazole

For the Day 14 assessments, subjects with a missing investigator assessment of clinical signs and symptoms, will have their missing values imputed using the method of multiple imputation. The missing values will be imputed using the following auxiliary information: region, treatment, baseline BMI, baseline age, and ethnicity. The procedure PROC MI will be used to generate 10 possible imputed datasets. Using these 10 multiple imputation datasets, determination of meeting the secondary endpoint of resolved acute VVC infection at Day 14 will be derived. Then, these 10 multiple imputation datasets containing the secondary endpoint of resolved acute VVC infection for each subject will be used to calculate the proportion of subjects who have cleared their infection in each treatment arm and the difference between these proportions using PROC FREQ. PROC MIANALYZE will be used to combine these ten results to produce a single 95% confidence interval for the difference in proportions between the VT-1161 arm and the fluconazole arm.

For the first sensitivity analysis, any subjects with missing Day 14 assessments will be counted as not having resolved the acute VVC infection. The 95% confidence interval for the difference in proportions between the VT-1161 arm and the fluconazole arm will be presented.

For the second sensitivity analysis, subjects who did not complete the Day 14 assessment will be excluded from the analysis. The 95% interval for the difference in proportions between the VT-1161 arm and the fluconazole arm will be presented.

Endpoint = proportion of subjects with at least one culture-verified acute VVC episode with sign and symptoms score ≥ 3 during the Maintenance Phase (post Day 14 through Week 50)

All 5 sensitivity analyses for the primary endpoint will be applied to this secondary endpoint with the exception that for the sensitivity analyses of this endpoint, only data from Day 14 through Week 50 will be considered.

Endpoint = time to first recurrence of a culture-verified acute VVC episode with sign and symptoms score ≥3 during the Maintenance Phase (post Day 14 through Week 50)

The primary analysis for the time to first acute VVC episode during Maintenance Phase will censor any subjects who do not have a culture-verified acute VVC episode at their last non-missing assessment for signs and symptoms and culture. If a subject does not experience a culture-verified acute episode post Day 14 through Week 50, they will be censored at Week 50.

For the sensitivity analysis, subjects who discontinue the study early during the Maintenance Phase will be considered to have a culture-verified acute VVC episode at the next scheduled assessment after their last non-missing assessment, if there is no recurrence prior to discontinuation. The scheduled study day of that assessment will be used for the time to recurrence. For subjects with a missing signs and symptoms or culture result not due to COVID-19 prior to discontinuation, the subject will be considered to have an episode at the visit with the missing assessments. The scheduled study day of the missing assessment will be used for the time to recurrence.

A second sensitivity analysis will be performed on the endpoint of time to first known treatment for VVC or recurrence of acute VVC during the Maintenance Phase. Time will be calculated as:

> Earliest date between date of first culture-verified acute VVC episode and date of first known treatment for VVC – date of randomization + 1

Subjects with no known treatment or no recurrence will be censored at their last non-missing assessment. The analysis methods for the secondary endpoint of time to first recurrence will be used.

Endpoint = proportion of subjects with at least one positive culture for Candida species during the Maintenance Phase

The first 4 sensitivity analyses for the primary endpoint will be applied to this secondary endpoint with the exception that for the sensitivity analyses of this endpoint, only the culture data will be considered.

3.4.5. Derived and Transformed Data

There are no planned transformations of data.

3.4.6. Imputation of Incomplete Dates

An incomplete date is any date for which either the day, month or year is unknown, but not all 3 fields are unknown. An incomplete date occurs when the exact date an event occurred or ended cannot be obtained from a subject. For many of the analyses, a complete date is necessary to determine if the event should be included in the analysis (i.e., if the event is treatment-emergent) or to establish the duration of an event. In such cases, incomplete dates will be imputed.

For purposes of imputation of dates for Adverse Events and concomitant medications, all events with an incomplete end date are assumed to be on-going at the end of the study.

To minimize bias, the project statistician will impute dates in a systematic, reasonable manner. If the month/year is the same as the Day 1 month/year, then the date will be set to the date of Day 1. In other cases, missing days will be imputed as the day component of Day 1, missing months/years will be imputed as the month/year of Day 1. If the resulting imputed date is an invalid date, then the next valid date will be used (ex: 31FEB2019 will be 01MAR2019).

Duration will not be calculated for events with a partial start or stop date.

3.4.7. By-Study Visit Displays

When data are collected serially over time, individual data presentations may include by-study visit displays for all scheduled study visits. Visits will be presented according to the nominal visit as obtained from the electronic data collection system or laboratory data unless the visit is an unscheduled visit. Unscheduled visits will be windowed based on the Study Day at which they occurred as defined in section 3.4.8. An unscheduled visit will only be used if a scheduled visit is not available. If a subject has multiple non-missing scheduled values on the same date, then the last one is used, as determined by the time collected, if available. If time is not present and the subject has multiple non-missing scheduled values on the same date, the 'worst' value will be the one designated as the value used. If no scheduled values are available, an unscheduled visit may be used.

3.4.8. Visit Windows

The visits will be used as nominally recorded in the electronic data collection system. Unscheduled visits will be windowed based on the Study Day at which they occur but will only be used if the scheduled visit is not available. The exception to this will be for the primary and key secondary endpoints where an unscheduled visit with a culture-verified acute VVC episode with signs and symptoms of ≥3 will result in the subject being considered as a failure. Unscheduled visits will be windowed based on the table below:

Table 1: Visit Windows for Early Termination and Unscheduled Visits

Nominal Visit	***Visit Window***
Day 1	Study Day ≤ 1
Day 14	Study Day 12 to 16
Week 8	Study Day 49 to 63
Week 14	Study Day 84 to 112
Week 20	Study Day 126 to 154
Week 26	Study Day 168 to 196
Week 32	Study Day 210 to 238
Week 38	Study Day 252 to 280
Week 44	Study Day 294 to 322
Week 50	Study Day 336 to 364

3.4.9. Definitions and Terminology

Baseline Value
For purposes of analysis, the baseline value is defined as the last non-missing value obtained prior to initiation of IMP.

Day 1
Day 1 is defined as the date of first randomized IMP administration/dispensation.

Study Day
Study Day is defined relative to Day 1. Thus, the study day of an event is calculated as:

Study Day = ((event date – date of Day 1) + 1)

Study Visit
Study Visit is the nominal visit as recorded on the CRF.

Induction Phase
Induction phase will include all assessments done from randomization through Day 14.

Maintenance Phase
Maintenance Phase will include all assessments performed from post Day 14 through Week 50 or early termination.

Days on Maintenance
Days on Maintenance is calculated as:

Number of Days on Maintenance = study discontinuation date – date of first day maintenance IMP was taken + 1

Last Dose of IMP
Last Dose of Study IMP is defined as the last date that the subject received IMP as determined by last date of dosing as recorded on the IMP administration panel of the CRF.

IMP Exposure (days)
IMP Exposure is defined as the number of days from Day 1 to the date of Last Dose of IMP.

IMP Compliance for the Induction Phase (first week of the study)
Number of daily doses taken will be the count of days the subject received a dose on Days 1 to 7. For the purpose of compliance calculation, doses that are marked as "Missed/Interrupted" or "Discontinued VT-1161 Permanently" will not be counted as a received dose. IMP Compliance is calculated as:

IMP Compliance = (Number of Daily Doses Taken)/ 4

IMP Compliance for the Maintenance Phase Weekly Dosing (Day 14 through Week 12 of the study)
Number of weekly doses taken will be the count of days the subject received a dose on Weeks 2 to 12. For the purpose of compliance calculation, doses that are marked as "Missed/Interrupted" or "Discontinued VT-1161 Permanently" will not be counted as a received dose. IMP Compliance is calculated as:

IMP Compliance = (Number of Weekly Doses Taken)/ 11

Days on Study
Days on Study is calculated as:

Number of Days on Study = study discontinuation date - informed consent date + 1

Age
The age is defined as the age value recorded in the electronic case report form.

Change from Baseline
Change from Baseline for a given endpoint is defined as the Study Day X Value minus the Baseline Value.

Acute VVC episode in Maintenance
Acute VVC episode in the Maintenance Phase (considered a recurrent episode) of the study is defined as having a total clinical signs and symptoms score ≥3 associated with a positive culture for Candida species.

Recurrent VVC
A history of RVVC is defined as 3 or more VVC episodes in the past 12 months.

Treatment-emergent Laboratory Abnormalities
A treatment-emergent laboratory abnormality is defined as a result in which the baseline value is within normal laboratory limits and the post-baseline value is outside normal laboratory limits. If the relevant baseline assessment is missing, then any post-baseline value outside normal laboratory limits is considered to be treatment-emergent.

Treatment-emergent Laboratory Toxicity
A treatment-emergent laboratory toxicity is defined as an increase of at least one toxicity grade from the baseline assessment at any post baseline visit. If the relevant baseline assessment is missing, then any graded abnormality (i.e., at least Grade 1) is considered to be treatment-emergent.

Adverse Event
An AE is any untoward, undesired, unplanned clinical event in the form of signs, symptoms, disease, or laboratory or physiological observations occurring in a human participating in a clinical study with a Mycovia Pharmaceuticals, Inc. product, regardless of causal relationship. A "pre-existing" condition is one that is present prior to the start of IMP administration and is reported as part of the subject's medical history. Pre-existing conditions should be reported as AEs only if the frequency, intensity, or character of the pre-existing condition worsens after the start of IMP.

Laboratory abnormalities generally are not considered AEs unless they are associated with clinical signs or symptoms or require medical intervention. A laboratory abnormality (e.g., a clinically significant change detected on clinical chemistry, hematology, urinalysis) that is independent from a known underlying medical condition and that requires medical or surgical intervention, or leads to IMP interruption or discontinuation, must be considered an AE.

Treatment-Emergent Adverse Event
Any recorded Adverse Event that occurs on or after the initiation of IMP is considered treatment-emergent. Additionally, it is assumed that an Adverse Event which was reported to have started on Day 1 without an associated onset time may have occurred after the initiation of IMP. Hence, Adverse Events occurring on Day 1 are assumed to be treatment-emergent.

Concomitant Medications
Concomitant medications are those medications taken on or after the initiation of IMP. This definition includes medications started prior to the initiation of IMP but continuing concomitantly with IMP.

Prior Medications
Prior medications are those medications taken prior to the initiation of IMP but stopped before initiation of IMP.

3.5. TIMING OF ANALYSES

The final analysis will be conducted once the last subject completes or discontinues the study, and the resulting clinical database has been cleaned, quality checked, the pre-analysis meeting has occurred, and the database has been locked.

4. ANALYSIS POPULATIONS

The populations for analysis will include Intent-to-Treat (ITT), Modified ITT (mITT), Safety, Per Protocol (PP), and Induction Phase PP.

4.1. INTENT-TO-TREAT POPULATION

The ITT population is defined as all randomized subjects.

The ITT population will be the primary population for the primary and the secondary endpoints except for the key secondary endpoint of the proportion of subjects with resolved acute VVC infections (clinical signs and symptoms score of <3) at Day 14 following treatment with VT-1161 or fluconazole.

4.2. MODIFIED INTENT-TO-TREAT POPULATION

The mITT population is defined as all randomized subjects who:

- had a positive central KOH at Screening,
- had a positive culture at Screening,
- had a negative culture at Day 14.

The Induction Phase mITT population is defined as all randomized subjects who:

- had a positive central KOH at Screening,
- had a positive culture at Screening.

4.3. SAFETY POPULATION

The safety population is defined as all randomized subjects who receive at least 1 dose of IMP.

4.4. PER-PROTOCOL POPULATION

The PP population is defined as all randomized subjects who:

- had no deviations to inclusion/exclusion criteria that could impact treatment outcome.
- were compliant with the assigned study treatment, defined as ≥80% compliant during the Induction Phase and ≥50% compliant during the Maintenance Phase
- had the Week 50 visit completed within the acceptable time window (±14 days)
- had no major protocol violations that would impact treatment outcome.

The Induction Phase PP population is defined as all randomized subjects who:

- had no deviations to inclusion/exclusion criteria that could impact treatment outcome during the Induction Phase.
- were compliant with the assigned study treatment during the Induction Phase, defined as ≥80% compliant during the Induction Phase
- had no major protocol violations that would impact treatment outcome during the Induction Phase

Mycovia will review all protocol violations to determine which subjects should be removed from the Per Protocol populations prior to the blind being broken. The output from this review, including the date(s) the meetings were held, the data reviewed, and the decisions made will be documented and placed into the study files.

The Induction Phase PP population will be the primary population for the key secondary efficacy endpoint of the proportion of subjects with resolved acute VVC infections (clinical signs and symptoms score of <3) at Day 14 following treatment with VT-1161 or fluconazole.

5. STATISTICAL METHODS

Descriptive statistical methods will also be used to summarize the data from this study, with hypothesis testing performed for the primary and key secondary efficacy endpoints. Unless stated otherwise, the term "descriptive statistics" refers to number of subjects, mean, median, standard deviation, minimum, and maximum for continuous data, and frequencies and percentages for categorical data. For categorical variables, the denominator of percentages will be the number of subjects in the treatment group, except for those collected by study visit and/or scheduled time point, in which case the denominator of percentages will be the number of subjects with a non-missing value at the visit and/or the scheduled time point.

All data collected during the study will be included in data listings. Unless otherwise noted, the data will be sorted first by treatment group, subject number, and then by date within each subject number.

The term 'treatment group' refers to VT-1161 and fluconazole/Placebo groups.

All statistical testing will be two-sided and will be performed using a significance (alpha) level of 0.05 unless otherwise stated (see Section 3.4.3). P-values will be presented to three decimal places. For the efficacy endpoints, the VT-1161 treatment group will be tested versus fluconazole/placebo via statistical inference. [redacted]

The statistical analyses will be conducted with the SAS® software package version 9.4 or higher. All analyses will be subject to formal verification procedures. Specifically, results will be independently verified by a second programmer/statistician prior to issuance of the draft statistical report. All documents will be reviewed by the lead statistician to ensure accuracy and consistency of analyses.

5.1. SUBJECT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Subject disposition consisting of the number of subjects screened, randomized, included in each analysis population, completed the study, and discontinued from the study will be provided. The reasons for early discontinuation will be presented by treatment group. Additionally, the number of days on study, the number of days on IMP, the number of days on IMP during the Induction Phase, the number of days on IMP during the Maintenance Phase, and the number of days in the Maintenance Phase will be summarized for all treated subjects. A consort diagram of subject disposition will be produced.

Demographic data and screening/baseline characteristics including age, race, ethnicity, height, weight, body mass index, and number of acute VVC episodes in the previous 12 months will be summarized using statistics for the ITT population. This information will be reviewed for baseline differences, but no statistical testing will be performed. All data above, along with date of birth and medical/surgical history, will be listed.

IMP compliance for the Induction Phase and the Maintenance Phase will also be summarized by treatment group.

5.2. EFFICACY ANALYSIS

All primary and key secondary efficacy analyses will be performed on the ITT, mITT, and PP Populations except for the key secondary endpoint of the proportion of subjects with resolved acute VVC infections (clinical signs and symptoms score of <3) at Day 14 which will be performed on the Induction Phase PP, ITT, and Induction Phase mITT Populations. [redacted]

[redacted]

5.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint for the study is:

- The proportion of subjects with one or more culture-verified acute VVC episodes (post randomization through Week 50) in the ITT population, which includes subjects with an unresolved VVC episode during the Induction Phase (post-randomization through Day 14). An acute VVC episode (considered a recurrent episode) is defined as a positive culture for Candida species and a clinical signs and symptoms score of ≥3.

5.2.1.1. Primary Efficacy Analysis

The primary method of analysis is a Chi-square test for active treatment versus placebo based on the ITT population. See Section 3.4.4 for details on how subjects will be classified. [redacted]

The number and percentage of subjects with one or more culture-verified acute VVC episodes with signs and symptoms of ≥3 post randomization through Week 50 will be summarized across treatment groups. The percentages will also be plotted by treatment group.

[redacted]

5.2.2. Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints for the study are:

- The proportion of subjects with resolved acute VVC infections (clinical signs and symptoms score of <3) at Day 14 following treatment with VT-1161 or fluconazole.
- The proportion of subjects with at least one culture-verified acute VVC episode with signs and symptoms ≥3 during the Maintenance Phase (post Day 14 through Week 50).

- Time to first recurrence of a culture-verified acute VVC episode with signs and symptoms score ≥3 during the Maintenance Phase (post Day 14 through Week 50).
- The proportion of subjects with at least one positive culture for Candida species during the Maintenance Phase (post Day 14 through Week 50)

5.2.3. Key Secondary Efficacy Analysis

The proportion of subjects with resolved acute VVC infections at Day 14 following treatment with VT-1161 or fluconazole will be summarized by treatment. The proportion of subjects with resolved acute VVC infections at Day 14 following treatment with VT-1161 will be evaluated for non-inferiority versus the fluconazole arm using the Induction Phase PP population. A non-inferiority margin of 15% will be used. If the lower limit of the 95% confidence interval for the difference in proportions between the VT-1161 arm and the fluconazole arm is greater than -15% then non-inferiority will be claimed. For the primary analysis of this endpoint, subjects with missing Day 14 clinical signs and symptoms score will be imputed using MI. [redacted]

The proportion of subjects with at least one culture-verified acute VVC episode with signs and symptoms ≥ 3 during the Maintenance Phase (post Day 14 through Week 50) will be summarized across treatment groups and will be analyzed using a similar method as the primary efficacy outcome. Subjects who failed to clear their acute infection during the Induction Phase will be excluded from this analysis.

Time to recurrence of acute VVC during the Maintenance Phase (post Day 14 though Week 50) will be estimated using the method of Kaplan-Meier. Time will be calculated as:

Date of first culture-verified acute VVC episode – date of randomization + 1

Subjects with no recurrence will be censored at their last non-missing assessment (see section 3.4.4 on missing data). The number of subjects censored, mean, standard error, median, 95% CI for the median and Q1 and Q3 of the time to recurrence will be presented. Difference between treatment groups will be assessed using a log-rank test. Subjects who failed to clear their acute infection during the Induction Phase will be excluded from this analysis.

The proportion of subjects with one or more positive cultures for Candida species post Day 14 through Week 50 will be summarized across treatment groups. A chi-square test will be used to compare the active treatment group to placebo. Subjects who failed to clear their acute infection during the Induction Phase will be excluded from this analysis.

Inferences resulting from the above analyses will be subject to controlling for type I error as described in Section 3.4.3.

[redacted]

[redacted]

[redacted]

5.2.6. Graphical Displays

The number and percentage of the primary and binary secondary efficacy endpoints will be plotted on separate bar graphs across treatment groups with 95% confidence intervals. A Kaplan-Meier

plot of time to first recurrence of a culture-verified acute VVC during the maintenance phase will be generated by treatment group.

5.3. SAFETY

All safety analyses will be performed on the Safety Population.

5.3.1. Adverse Events

Adverse events will be mapped to a Medical Dictionary for Regulatory Activities version 21 or higher by preferred term and system organ classification. Within a study phase (induction, maintenance), if a subject experiences multiple events that map to a single preferred term, the greatest severity grade and strongest investigator assessment of relation to study medication observed will be assigned to the preferred term for the appropriate summaries. Should an event have a missing severity or relationship, it will be classified as having the highest severity and/or strongest relationship to study medication. The occurrence of treatment-emergent adverse events (TEAEs) will be summarized by treatment group using preferred terms, system organ classifications, and greatest severity. Separate summaries of treatment-emergent SAEs, TEAEs related to IMP as evaluated by the investigator, TEAEs related to IMP as evaluated by Mycovia, and events leading to the discontinuation of IMP will be generated. TEAEs will be summarized overall and by treatment group. All adverse events reported will be listed for individual subjects showing both verbatim and preferred terms. All adverse events that occurred prior to the initiation of IMP will be excluded from the tables but will be included in the listings.

Missing onset dates will be imputed as previously outlined in Section 3.4.6 as required to determine TEAEs.

5.3.2. Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization dictionary (Version: March 2018). Concomitant medications will be summarized by frequency of generic drug name. Prior and concomitant medications will be presented in a data listing.

5.3.3. Clinical Laboratory Assessments

Descriptive summaries of quantitative clinical laboratory results (hematology, chemistry, and urinalysis) and their change from baseline values will be presented by study visit and treatment group. Observed values of categorical urinalysis data will be displayed with frequencies and percentages. All laboratory data will be listed for individual subjects.

Treatment-emergent abnormal laboratory toxicities will be identified. These abnormalities will be graded according to the Division of Microbiology and Infectious Diseases Adult Toxicity Table. If a laboratory value is not addressed in the Division of Microbiology and Infectious Diseases Adult Toxicity Table, then the most recent version of the Common Terminology Criteria for Adverse Events, version 4.0 published by the National Cancer Institute will be used.

Frequency and percentage of subjects experiencing at least one treatment-emergent graded toxicity will be summarized by study visit and treatment group. The number and percentage of subjects

having a Grade 3 or 4 treatment-emergent graded toxicity will also be presented by study visit and treatment. Additionally, a shift table of the number and percentage of subjects with each toxicity grade at baseline value to each study visit toxicity grade, as well as worst overall toxicity grade will be presented by treatment group.

Treatment-emergent laboratory abnormalities will also be identified. The number and percentage of subjects having each abnormality will be presented by study visit and treatment group.

5.3.4. Other Safety Analyses

Descriptive summaries of vital signs and their change from baseline will be presented by study visit and treatment group and all vital signs will be listed.

Physical examination findings will be listed.

ECG measurements will include heart rate, QT interval, Fridericia-corrected QT interval (QTcF), PR interval, and QRS interval. Change from baseline will be summarized descriptively by treatment group at each scheduled evaluation and all ECG data will be listed. Proportion of subjects with abnormal ECG interpretations will be summarized at each study visit and by treatment group. Proportion of subjects who meet each of the following criteria from International Conference on Harmonization Guideline E14 "Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs" (October 2005) for QT and corrected QT intervals will be summarized across treatment groups:

- QTcF >450 msec
- QTcF >480 msec
- QTcF >500 msec
- QTcF increases from baseline by ≥30 msec
- QTcF increases from baseline by ≥60 msec

6. PROTOCOL VIOLATIONS

Possible protocol deviations will be identified and displayed in a data listing and sorted by treatment group, subject, and study day (where applicable). In addition, the following deviations may be identified and classified as a protocol violation from the database:

- Missing efficacy assessments
- Violations of inclusion/exclusion criteria
- Non-compliance with IMP

All protocol violations, including the ones identified by statistics, will be reviewed by the Medical Monitor and appropriate study team members prior to unblinding, as stated in section 4.4. There will be a face-to-face meeting to discuss all subjects that have been removed from the per-protocol population programmatically. A document will be provided for the meeting detailing the criteria not met for each subject. All protocol deviations will be listed. Separate listings will be presented for subject level deviations and site level deviations.

7. PHARMACOKINETICS

Analyses of plasma concentration data will be performed using the safety population. Descriptive summaries, including coefficient of variation, will be presented by study visit and treatment group and all concentration data will be listed. For the descriptive summaries, values below LLOQ will be set to 0 for the summary calculations. A plot of the mean concentration by time will be produced for the VT-1161 treatment group. If a serial PK analysis is performed, data will be analyzed separately and included as an appendix to the final study report.

8. CHANGES IN THE PLANNED ANALYSES

There are no changes in the planned analyses.

9. REVISION HISTORY

Date	Revision	Rationale
23SEP2020	Updated sensitivity analyses so that missing data due to a missed visit because of COVID-19 are not treated as a recurrence	Since subjects may have been unable to go to the site for their scheduled visits during the COVID-19 pandemic due to sites being closed or shelter at home requirements, there is a known reason for the missing data and as such these will not be treated as recurrences.
	Updated missing date imputation rules to be the next valid date for cases where an imputed date is an invalid date.	Since invalid imputed dates are possible (ex. February 31st), imputation rule was updated to ensure the next valid date is used as the imputed date for these situations (ex. February 31st would have an imputed date of March 1st.
	Updated compliance calculation	Number of pills returned is not collected in the eCRF. Definition was updated per the information that was collected.
	Updated to use age as collected in the eCRF	Since only birth year is captured for all subjects, updated to use age as collected instead of calculating age.
	Removed exact 95% CI for key secondary endpoints and switched from Fisher's exact test to a Chi-square test.	The primary endpoint is derived based on signs and symptoms and culture results where missing values are imputed using MI. The key secondary endpoints will use the imputed results that are used for the primary endpoint derivation and will use similar analysis methods as the primary endpoint and as such, the exact 95% CI will not be computed, and a chi-square test will be used instead of a Fisher's exact test.
	[redacted]	[redacted]

	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	Added summary of TEAE related to IMP as evaluated by Mycovia	Mycovia also evaluated adverse event relatedness to IMP.
	Concomitant medication summary changed from frequency of Anatomical Therapeutic Chemical classification and generic drug name to frequency of generic drug name.	ATC coding is not being performed.

	Added summary, plot, and listing of concentration data	Included summary, figure, and listing for concentration data with the other SAP defined analyses as opposed to including it in a separate PK report.
	Updated handling of missing data in efficacy section 5.2.3 to state that primary efficacy analysis will impute missing signs and symptoms score using MI.	Section 5.2.3 was updated to be consistent with section 3.4.4.
	Clarified primary population as the Induction Phase PP population for the key secondary efficacy endpoint of the proportion of subjects with resolved acute VVC infections at Day 14.	Per the FDA guidance on non-inferiority trials, using the ITT population could bias the results towards the alternative hypothesis. Using the Induction Phase PP population should reduce this bias.
	[redacted]	[redacted]
		[redacted]
21DEC2020	Updated non-inferiority margin justification for key secondary endpoint [redacted]	Additional fluconazole data is available from studies VMT-VT-1161-CL-011 and VMT-VT-1161-012. New data is available for the placebo rate based on 2 Phase 3 Scynexis studies.

	Added Induction Phase PP mITT Population	Added mITT Population for the acute infection endpoints to be consistent with the mITT Population definition in the FDA guidance for the treatment of VVC
	Updated planned populations for the analyses of the acute VVC infection	Included analyses on the Induction Phase mITT population for the following acute infection endpoints: resolved acute VVC infection (clinical signs and symptoms score of < 3) at Day 14, clinical cure (clinical signs and symptoms score of 0) at Day 14, and clinical signs and symptoms score of 0 and negative culture for Candida species at Day 14.
	Added consort diagram	Included a consort diagram to show a visual of the disposition table
	Added listing for site level deviations	Split the planned deviation listing into 2 listings, one for subject level deviations and one for site level deviations

10. PROGRAMMING CONVENTIONS

- Page orientation, margins, and fonts: Summary tables, listings, and figures will appear in landscape orientation. There should be a minimum of a 0.5" boundary on the upper (bound) and lower edge, and a minimum of a 0.75" boundary on the right and left edges. Output should be printed in Courier New with a point size of 8. Titles should be printed using Arial point size 10.
- Identification of analysis population: Every summary table and figure should clearly specify the analysis population being summarized. Listings will be prepared for all subjects enrolled.
- Group headers: In the summary tables, the group headers will identify the summary group and the within-group sample size for the indicated analysis population. Of note, the header's sample size does not necessarily equal the number of subjects actually summarized within any given summary module; some subjects in the analysis population may have missing values and thus may not be summarized.
- Presentation of sample sizes: Summary modules should indicate, in one way or another, the number of subjects actually contributing to the summary statistics presented in any given summary module. As mentioned above, this may be less than the number of subjects in the analysis population.
    - In the quantitative modules describing continuous variables (and thus presenting sample size, means, and standard deviations), the sample size should be the number of non-missing observations
    - For categorical variables that are presented in frequency tables, the module should present the total count in addition to the count in each category. Percentages should be calculated using this total as the denominator, and the percentage corresponding to the sum itself (that is, 100%) should be presented so as to indicate clearly to a reviewer the method of calculation.
- Sorting: Listings will be sorted by summary group, subject number and date, if applicable. If a listing is sorted in a different manner, a footnote will indicate as such.
- General formatting rules: Rounding for all variables will occur only as the last step, immediately prior to presentation in listings, tables, and figures. No intermediate rounding will be performed on derived variables. The standard rounding practice of rounding numbers ending in 0-4 down and numbers ending in 5-9 up will be employed.
- The presentation of numerical values will adhere to the following guidelines:
    - Raw measurements will be reported to the number of significant digits as captured electronically or on the CRFs.
    - Standard deviations will be reported to one decimal place beyond the number of decimal places the original parameter is presented.
    - Means will be reported to the same number of significant digits as the parameter.
    - Calculated percentages will be reported with no decimals.

- Dates will be formatted as DDMMMYYYY. Partial dates will be presented on data listings as recorded on CRFs.
    - Time will be presented according to the 24-hour clock (HHMM).

11. PROPOSED TABLES, LISTINGS, AND FIGURES FOR FINAL ANALYSIS

Summary Tables and Figures

Accountability and Baseline Characteristics

14.1.1.1	Subject Disposition, All Subjects
14.1.1.2	Consort Diagram, All Subjects
14.1.2.1	Demographics and Baseline Characteristics, ITT Population
14.1.2.2	Demographics and Baseline Characteristics, PP Population
14.1.3.1	IMP Compliance, ITT Population
14.1.3.2	IMP Compliance, PP Population
14.1.3.3.1	Pharmacokinetics, Safety Population

Efficacy

14.2.1.1	Proportion of Subjects with One or More Culture-Verified Acute VVC Episode, ITT Population
14.2.1.3	Proportion of Subjects with One or More Culture-Verified Acute VVC Episode, mITT Population
14.2.1.4	Proportion of Subjects with One or More Culture-Verified Acute VVC Episode, PP Population
14.2.1.5	Proportion of Subjects with One or More Culture-Verified Acute VVC Episode – Sensitivity Analysis Results, ITT Population
14.2.1.6	Proportion of Subjects with One or More Culture-Verified Acute VVC Episode by Subgroup, ITT Population
14.2.1.7	Logistic Regression for Primary Endpoint, ITT Population
[redacted]	[redacted]
14.2.2.1.1	Proportion of Subjects with Resolved Acute VVC Infections at Day 14, Induction Phase PP Population
14.2.2.1.3	Proportion of Subjects with Resolved Acute VVC Infections at Day 14, ITT Population
14.2.2.1.4	Proportion of Subjects with Resolved Acute VVC Infections at Day 14, Induction Phase mITT Population
14.2.2.1.5	Proportion of Subjects with Resolved Acute VVC Infections at Day 14 – Sensitivity Analysis Results, Induction Phase PP Population
14.2.2.1.6	Proportion of Subjects with Resolved Acute VVC Infections at Day 14 by Subgroup, Induction Phase PP Population
14.2.2.2.1	Proportion of Subjects with One or More Culture-Verified Acute VVC Episode During the Maintenance Phase (Post Day 14 through Week 50), ITT Population
14.2.2.2.3	Proportion of Subjects with One or More Culture-Verified Acute VVC Episode During the Maintenance Phase (Post Day 14 through Week 50), mITT Population

14.2.2.2.4	Proportion of Subjects with One or More Culture-Verified Acute VVC Episode During the Maintenance Phase (Post Day 14 through Week 50), PP Population
14.2.2.2.5	Proportion of Subjects with One or More Culture-Verified Acute VVC Episode During the Maintenance Phase (Post Day 14 through Week 50) – Sensitivity Analysis Results, ITT Population
14.2.2.2.6	Proportion of Subjects with One or More Culture-Verified Acute VVC Episode During the Maintenance Phase (Post Day 14 through Week 50) by Subgroup, ITT
14.2.2.3.1	Time to First Recurrence of Culture-Verified Acute VVC During the Maintenance Phase (Post Day 14 through Week 50), ITT Population
14.2.2.3.3	Time to First Recurrence of Culture-Verified Acute VVC During the Maintenance Phase (Post Day 14 through Week 50), mITT Population
14.2.2.3.4	Time to First Recurrence of Culture-Verified Acute VVC During the Maintenance Phase (Post Day 14 through Week 50), PP Population
14.2.2.3.5	Time to First Recurrence of Culture-Verified Acute VVC During the Maintenance Phase (Post Day 14 through Week 50) – Sensitivity Analysis Results, ITT Population
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12. APPENDIX 1: SCHEDULE OF EVENTS/STUDY VISITS

Activities	Screening Day 1 (±2 days)	Day 2[i]	Day 14 (±2 days) Initial TOC	Week 8 (±7 days)	Week 14 (±14 days) EOT	Week 20 (±14 days)	Week 26 (± 14 days)	Week 32 (± 14 days)	Week 38 (± 14 days)	Week 44 (± 14 days)	Week 50 (± 14 days) EOS	Unscheduled Visit[j]
Sign Informed Consent and/ or Assent Form	X											
Inclusion/ Exclusion Criteria	X											
Medical/Surgical History	X											
Prior/Concomitant Medications/ Treatments[a]	X	X	X	X	X	X	X	X	X	X	X	X
Collect and record AEs		X	X	X	X	X	X	X	X	X	X	X
Body Height and Weight	X				X[b]		X[b]				X[b]	
Vital Signs[c]	X		X	X	X	X	X	X	X	X	X	X
Physical and Vaginal Examination	X		X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]
Clinical Signs & Symptoms of Vulvovaginitis	X		X	X	X	X	X	X	X	X	X	X
Local KOH Wet Mount	X											X
Central Vaginal Fungal Culture	X		X	X	X	X	X	X	X	X	X	X
ECG	X		X		X		X				X	
PK Samples[e]	X	X	X		X						X	
Clinical Laboratory Samples[f]	X		X	X	X	X	X	X	X	X	X	X
Urinalysis	X		X		X		X		X		X	
Hematology (CBC with differential)	X		X		X		X		X		X	
HIV Ab, HBsAg, anti-HCV	X											
Pregnancy Test[g] (WOCBP)	X				X		X				X	
Randomization	X											
Administer VT-1161 or Fluconazole[h]	X	X										
Administer VT-1161 or Placebo			X									
Review IMP[h]			X	X	X							

Abbreviations noted above - AEs: adverse events; CBC, complete blood count; ECG: electrocardiogram; EOS: End of Study; EOT: End of Treatment; HBsAg: Hepatitis B surface antigen; HCV: Hepatitis C virus; HIV: human immunodeficiency virus; IMP: investigational medicinal product; KOH: potassium hydroxide prep; PK: pharmacokinetic; TOC: Test of Cure; WOCBP: women of childbearing potential.

a. All medication taken 30 days prior to Screening and all non-pharmacologic treatments received 72 hours prior to Screening will be recorded through the EOS visit.
b. Weight only
c. Vital signs include sitting heart rate, blood pressure, temperature, and respiratory rate.
d. Limited Physical Examination, i.e. vaginal speculum examination plus a symptom-directed physical examination
e. Subjects participating in the intense Day 1 and Day 2 PK collection will have samples taken predose and 1, 2, 4, and 8 hours after dosing. All subjects will have PK draws prior to IMP on Day 14 and Week 14 and at Week 50.
f. Serum chemistry (creatinine, BUN, ALT, AST, alkaline phosphatase, total bilirubin, conjugated bilirubin, albumin, total protein, total carbon dioxide, glucose, sodium, potassium, chloride, calcium, and phosphorus, and creatine phosphokinase [CK], cholesterol, and triglycerides). Testing for HbA1c is performed only in known or suspected diabetic subjects at Screening. Cultures for testing for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* will be taken at Screening and sent to the central lab. Testing for *bacterial vaginosis* will be done locally at Screening. An OSOM® Rapid test or similar test will be performed for *Trichomonas vaginalis* locally at Screening.
g. For WOCBP, a local lab urine and central lab serum pregnancy test will be obtained at the Screening Day 1 visit. A central lab serum pregnancy test will be performed at Weeks 14, 26, and 50.
h. IMP is to be administered within 30 minutes after the subject's main meal of the day (as determined by the subject) at approximately the same time of the day consistently throughout the study. Approximately 240 mL (approx. 8 oz.) of water is to be consumed with each dose of IMP. Subject will be randomized to receive either 600mg VT-1161 (4 x 150 mg capsules) on Day 1 and 450 mg VT-1161 (3 x 150 mg capsules) on Day 2 followed by 11 weekly doses of 150 mg VT-1161, or 3 sequential 150 mg oral doses (every 72 hours) of over-encapsulated fluconazole followed by 11 weekly doses of placebo. In the Induction Phase, IMP may be over-encapsulated and matching placebo capsules will be provided to maintain study blind. Subjects participating in the intense PK collection will be required to take the Days 1 and 2 IMP at the Investigational Site. Remind subject to bring IMP to each visit to assess compliance.
i. Only subjects participating in the intense PK will come in for the Day 2 visit.
j. All procedures listed are to be completed only for unscheduled visits where a recurrent VVC episode is suspected. If the unscheduled visit is for repeat procedures (i.e., ECG, safety labs, etc.), only those specific procedures need to be performed, along with collection of any changes in medical treatments or medications and collection of any AEs.