PRS COVER PAGE for STATISTICAL ANALYSIS PLAN

TITLE: 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-011)

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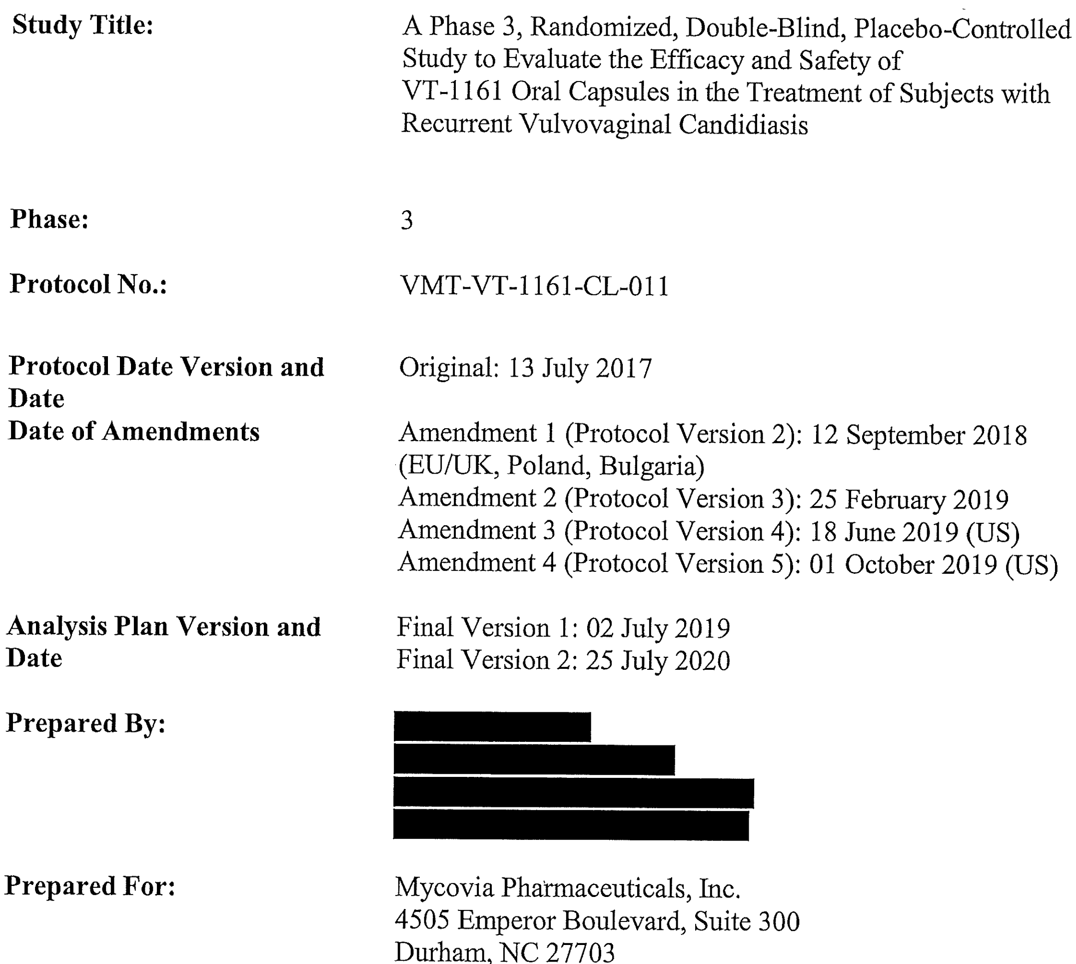
STATISTICAL ANALYSIS PLAN



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CONFIDENTIAL AND PROPRIETARY INFORMATION

STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

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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-011. 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. Details of separate analyses performed on any subgroup cohort will be documented in an addendum to the Statistical Analysis Plan. The planned analyses of the long-term extension data will be described in an addendum to the Statistical Analysis Plan.

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 compared to placebo in the treatment of subjects with recurrent vulvovaginal candidiasis (RVVC). The study consists of two phases: 1) an open-label Induction Phase for the treatment of the acute vulvovaginal candidiasis (VVC) episode with 3 sequential 150 mg oral doses (every 72 hours) of fluconazole, and 2) a Maintenance phase in which subjects will be randomly assigned in a 2:1 ratio (active to placebo) to receive either 1) a 150 mg daily dose of VT-1161 for 7 days followed by a 150 mg weekly dose of VT-1161 for 11 weeks, or 2) a matching placebo regimen for 12 weeks. The maintenance phase will include follow-up for each subject through Week 48.

Once subjects have provided informed consent or assent (as applicable), the investigational site will evaluate all subjects by completing a review of pertinent medical history, obtaining vital signs, height and weight, 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 or Gram stain 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 ≥3 and a positive local KOH wet mount or Gram stain 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 enter the Induction Phase. During the Induction Phase, the presenting acute VVC episode will be treated with 3 sequential 150 mg oral doses (every 72 hours) of fluconazole. Subjects will return approximately 14 days after the first dose of fluconazole for evaluation and, if the acute VVC episode has resolved (defined by a signs and symptoms score of <3), they will be randomized in a 2:1 ratio to receive either VT-1161 or a matching placebo regimen. Day 1 (Baseline) 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.

Vulvovaginal signs and symptoms will be evaluated at Screening and at each subsequent study visit. A local mycological assessment using KOH wet mount or Gram stain 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 Baseline, Day 14, Weeks 12, 24, 36, 48 and at unscheduled visits. Subject safety will be monitored by the reporting of adverse events 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
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
MCS	mental component score
PCS	physical component score
PK	pharmacokinetic
PP	per-protocol
PRO	patient reported outcome
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
mITT	modified intent to treat

2. OBJECTIVES

Primary:

- To evaluate the efficacy of oral VT-1161 in the treatment of RVVC through Week 48.

Secondary:

- To evaluate the safety and tolerability of oral VT-1161 in the treatment of RVVC through Week 48.
- To evaluate the impact of oral VT-1161 treatment on patient-reported outcomes through Week 48.

3. GENERAL STATISTICAL CONSIDERATIONS

3.1. PRIMARY STUDY HYPOTHESIS

The null hypothesis for this study is that the proportion of subjects with one or more culture-verified acute VVC episodes during the Maintenance Phase (post randomization through Week 48) 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 during the Maintenance Phase (post randomization through Week 48) 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.

3.2. SAMPLE SIZE

For the primary efficacy endpoint determination, a sample size of 68 active subjects and 34 placebo subjects provides at least 95% power to detect a treatment difference of 35% between the VT-1161 treatment group and the 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 48). (PASS 2008: Fisher's exact test, two-sided alpha=0.05, and assuming 50% of placebo subjects have recurrence). Based on an estimated 20% discontinuation rate, approximately 128 total subjects (85 active, 43 placebo) will be necessary for randomization to arrive at approximately 102 evaluable subjects.

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-011 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 pick up at least a 35% separation between the treatment groups.

While 102 total subjects will provide more than 90% power to detect reasonable differences between treatment groups in most of the pre-specified key secondary endpoints (see Sections 3.4.3 and 5.2.2), a sample size of 160 active subjects and 80 placebo subjects is needed to provide 80% power to detect a treatment difference of 3.9 between the VT-1161 treatment group and the placebo group in the change from screening through Week 48 in the SF-36 mental composite score (MCS) with a standard deviation of 10 points. (PASS 2008: two-sample t-test, alpha = 0.05). Therefore, with the expected discontinuation rate, approximately 300 subjects will be necessary for randomization to arrive at approximately 240 evaluable subjects.

Approximately 600 subjects will be screened to randomize approximately 300 subjects that would meet the inclusion/exclusion criteria.

3.3. RANDOMIZATION AND BLINDING

A total of approximately 300 eligible subjects will be randomized in a 2:1 ratio to either VT-1161 or 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 Baseline (Day 1) 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.

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 1. In addition, the primary efficacy endpoint will be analyzed for subjects with 4 or more historic VVC episodes.

3.4.3. Multiple Testing and Comparisons

The primary endpoint is the proportion of subjects with one or more culture-verified acute VVC episodes during the Maintenance Phase (post randomization through Week 48) in the intent-to-treat (ITT) population.

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.

Hierarchy of key secondary efficacy endpoints:

- Time to first recurrence of a culture-verified acute VVC episode with signs and symptoms score ≥3 during the Maintenance Phase.
- The proportion of subjects with at least one positive culture for Candida species during the Maintenance Phase.
- The proportion of subjects with at least one culture-verified acute VVC episode with signs and symptoms score ≥3 during post randomization through Week 24.
- Change from Screening through Week 48 in the SF-36 mental component score (MCS).
- Change from Screening through Week 48 in the SF-36 patient reported outcome survey total score.

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 48 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 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 randomization through Week 48 (including unscheduled visits) 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 48. 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 48 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 48 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 48, who do not experience a culture-verified acute VVC episode and have both non-missing signs and symptoms data at Week 48 and non-missing culture data at Week 48 will be censored at the Week 48 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 48. 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 48 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 48 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 48 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 48 without a culture-verified acute VVC episode and without any missing data not due to COVID-19, will be censored at Week 48. Subjects who do not experience a culture-verified acute VVC episode post randomization through Week 48 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 48 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 = time to first recurrence of a culture-verified acute VVC episode with sign and symptoms score ≥3 during Maintenance Phase

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 randomization through Week 48, they will be censored at Week 48.

For the sensitivity analysis, subjects who discontinue the study early 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. 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.

Endpoint = proportion of subjects with at least one culture-verified acute VVC episode with sign and symptoms score ≥ 3 during post randomization through Week 24

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 data through Week 24 will be considered.

Endpoint = Change from Screening through Week 48 for SF-36 MCS and SF-36 total score

For the SF-36 endpoints, missing data for a given item on the instrument will be handled in accordance with the scoring algorithm for the SF-36 questionnaire. If there are still missing values after applying the imputations according to the scoring algorithm, the missing values will be imputed using last-observation-carried-forward (LOCF) prior to calculating the change from baseline value. One sensitivity analysis will be performed where missing data will be excluded.

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 in order 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 (AEs) 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 6	Study Day 35 to 49
Week 12	Study Day 70 to 98
Week 18	Study Day 112 to 140
Week 24	Study Day 154 to 182
Week 30	Study Day 196 to 224
Week 36	Study Day 238 to 266
Week 42	Study Day 280 to 308
Week 48	Study Day 322 to 350

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.

Screening (Day -14 +/- 2 days)
Screening (Day -14 +/- 2 days) is defined as the date of starting Induction Phase where eligible subjects take their first dose of fluconazole.

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

Study Day
Study Day is defined relative to Day 1 (Baseline). 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 Screening through pre-randomization on Day 1.

Maintenance Phase
Maintenance Phase will include all assessments performed from post-randomization on Day 1 through Week 48 or early termination.

Days on Maintenance

Days on Maintenance is calculated as:

Number of Days on Maintenance = study discontinuation date - randomization date + 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 Daily Dosing 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)/ 7

IMP Compliance for the Weekly Dosing Phase (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.

Region
Region is derived based on country. The following 3 regions will be utilized: North America, Europe, and Japan. The North America region consists of sites in the USA and Canada. All sites in Europe are in the European region. The Japan region consists of sites in Japan.

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.

Mental Component Score (MCS)
The MCS is derived as the average of the following 4 domain scores: role limitations due to emotional problems, energy/fatigue, emotional well-being, and social functioning. If 2 or more of the domain scores are missing, the MCS will be missing (Zhu et al, 2016).

Physical Component Score (PCS)
The PCS is derived as the average of the following 4 domain scores: physical functioning, role limitations due to physical health, pain, and general health. If 2 or more of the domain scores are missing, the PCS will be missing (Zhu et al, 2016).

SF-36 Total Score

The SF-36 total score is derived as the average of the 8 domain scores. If 3 or more of the domain scores are missing, the total score will be missing.

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 study drug 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 study drug.

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 study drug 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 ITT, Modified ITT (mITT), Safety, and 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 secondary endpoints.

4.2. MODIFIED INTENT-TO-TREAT POPULATION

The mITT population is defined as all randomized subjects who:

- had a positive central KOH or Gram stain at Screening,
- had a positive culture at Screening,
- had a negative culture at Baseline.

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 daily dosing phase and ≥50% compliant during the weekly dosing phase
- had the Week 48 visit completed within the acceptable time window (±14 days)
- had no major protocol violations that would impact treatment outcome.

Mycovia will review all protocol violations to determine which subjects should be removed from the Per Protocol analysis 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.

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 matching 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 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, and the number of days in the maintenance phase will be summarized for all treated subjects.

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 daily dosing phase and weekly dosing 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.

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 during the Maintenance Phase (post randomization through Week 48) in the ITT population. An acute VVC episode during the Maintenance phase (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.

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 48 will be summarized across treatment groups. The percentages will also be plotted by treatment group.

5.2.2. Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints for the study are:

- Time to first recurrence of a culture-verified acute VVC episode with signs and symptoms of ≥3 during the Maintenance Phase.
- The proportion of subjects with at least one positive culture for Candida species during the Maintenance Phase.
- The proportion of subjects with at least one culture-verified acute VVC episode with signs and symptoms of ≥3 post randomization through Week 24.
- Change from Screening through Week 48 in the SF-36 mental component score (MCS).
- Change from Screening through Week 48 in the SF-36 patient reported outcome survey total score.

5.2.3. Key Secondary Efficacy Analysis

Time to recurrence of acute VVC 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.

The proportion of subjects with one or more positive cultures for Candida species post randomization through Week 48 and the number and percentage of subjects with one or more culture-verified acute VVC episodes post randomization through Week 24 of the study will be summarized across treatment groups. A Chi-square test will be used to compare the active treatment group to placebo for each key secondary endpoint.

Screening, Week 48, and change from Screening to Week 48 for the SF-36 MCS and SF-36 total score will be summarized by treatment group. The change from baseline value for each endpoint will be analyzed with a repeated measure analysis of covariance (ANCOVA) model with fixed effects for treatment group, time point, treatment by time point interaction and baseline value and a random effect of subject. A compound symmetry covariance structure will be used. The least squares (LS) means for each treatment group from the repeated measures ANCOVA model will be presented along with the 95% CI for the LSMeans, the difference in LSMeans between treatment groups, the 95% confidence interval for the difference, and the p-value for the difference.

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

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.

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.

8. CHANGES IN THE PLANNED ANALYSES

The descriptive statistics of the odds ratio and exact 95% confidence intervals for the primary endpoint will not be produced.

9. REVISION HISTORY

Date	Revision	Rationale
31AUG2017	Added multiple imputation for missing data for the primary endpoint	Incorporation of feedback from the FDA for handling missing data for the primary endpoint.
[redacted]	[redacted]	[redacted]
02JUL2019	Updated for protocol amendments	Protocol amendment 1 was effective 12SEP2018 Protocol amendment 2 was effective on 25FEB2019 Protocol amendment 3 was effective on 18JUN2019
25JUL2020	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.
	Added definition of region	Since region is an auxiliary factor for the MI, the definition of region was added to the definition section.
	Added definitions for MCS, PCS, and SF-36 total score	Added definitions for the derivations of these key secondary [redacted] efficacy endpoints. MCS and PCS are derived using the definition from the article titled "Health-related quality of life as measured with the Short-Form 36 (SF-36) questionnaire in patients with recurrent vulvovaginal candidiasis.
	Removed exact 95% CI for key secondary	The primary endpoint is derived based on signs and symptoms and culture results where missing values

	endpoints and switched from Fisher's exact test to a Chi-square test.	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.

	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.

10. REFERENCES

Zhu YX, Li T, Fan SR, Liu XP, Liang YH, & Liu P. "Health-related quality of life as measured with the Short-Form 36 (SF-36) questionnaire in patients with recurrent vulvovaginal candidiasis". *Health and Quality of Life Outcomes*. 2016;14:65.

11. 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).

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

Summary Tables and Figures

Accountability and Baseline Characteristics

14.1.1	Subject Disposition, 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 During the Maintenance Phase, ITT Population
14.2.1.3	Proportion of Subjects with One or More Culture-Verified Acute VVC Episode During the Maintenance Phase, mITT Population
14.2.1.4	Proportion of Subjects with One or More Culture-Verified Acute VVC Episode During the Maintenance Phase, PP Population
14.2.1.5	Proportion of Subjects with One or More Culture-Verified Acute VVC Episode During the Maintenance Phase – Sensitivity Analysis Results, ITT Population
14.2.1.6	Proportion of Subjects with One or More Culture-Verified Acute VVC Episode During the Maintenance Phase by Subgroup, ITT Population
14.2.1.7	Logistic Regression for Primary Endpoint, ITT Population
14.2.2.1.1	Time to First Recurrence of Culture-Verified Acute VVC, ITT Population
14.2.2.1.3	Time to First Recurrence of Culture-Verified Acute VVC, mITT Population
14.2.2.1.4	Time to First Recurrence of Culture-Verified Acute VVC, PP Population
14.2.2.1.5	Time to First Recurrence of Culture-Verified Acute VVC – Sensitivity Analysis Results, ITT Population
14.2.2.1.6	Time to First Recurrence of Culture-Verified Acute VVC by Subgroup, ITT
14.2.2.2.1	Proportion of Subjects with At Least One Positive Culture During the Maintenance Phase, ITT Population
14.2.2.2.3	Proportion of Subjects with At Least One Positive Culture During the Maintenance Phase, mITT Population
14.2.2.2.4	Proportion of Subjects with At Least One Positive Culture During the Maintenance Phase, PP Population
14.2.2.2.5	Proportion of Subjects with At Least One Positive Culture During the Maintenance Phase – Sensitivity Analysis Results, ITT Population

14.2.2.2.6	Proportion of Subjects with At Least One Positive Culture During the Maintenance Phase by Subgroup, ITT Population
14.2.2.3.1	Proportion of Subjects with At Least One Culture-Verified Acute VVC Episode During Post Randomization Through Week 24, ITT Population
14.2.2.3.3	Proportion of Subjects with At Least One Culture-Verified Acute VVC Episode During Post Randomization Through Week 24, mITT Population
14.2.2.3.4	Proportion of Subjects with At Least One Culture-Verified Acute VVC Episode During Post Randomization Through Week 24, PP Population
14.2.2.3.5	Proportion of Subjects with At Least One Culture-Verified Acute VVC Episode During Post Randomization Through Week 24 – Sensitivity Analysis Results, ITT Population
14.2.2.3.6	Proportion of Subjects At Least One Culture-Verified Acute VVC Episode During Post Randomization Through Week 24 by Subgroup, ITT Population
14.2.2.4.1	Summary of SF-36 MCS and Change from Screening by Study Visit, ITT Population
14.2.2.4.2	Summary of SF-36 MCS and Change from Screening by Study Visit, mITT Population
14.2.2.4.3	Summary of SF-36 MCS and Change from Screening by Study Visit, PP Population
14.2.2.4.4	Summary of SF-36 MCS and Change from Screening by Study Visit - Sensitivity Analysis, ITT Population
14.2.2.5.1	Summary of SF-36 Total Score and Change from Screening by Study Visit, ITT Population
14.2.2.5.2	Summary of SF-36 Total Score and Change from Screening by Study Visit, mITT Population
14.2.2.5.3	Summary of SF-36 Total Score and Change from Screening by Study Visit, PP Population
14.2.2.5.4	Summary of SF-36 Total Score and Change from Screening by Study Visit - Sensitivity Analysis, ITT Population
14.2.3.1.1	Summary of SF-36 PCS and Change from Screening by Study Visit, ITT Population
14.2.3.1.2	Summary of SF-36 PCS and Change from Screening by Study Visit, mITT Population
14.2.3.2.1	Summary of SF-36 Domain Scores and Change from Screening by Study Visit, ITT Population
14.2.3.2.2	Summary of SF-36 Domain Scores and Change from Screening by Study Visit, mITT Population
14.2.3.3.1	Summary of Acute VVC by Study Visit, ITT Population
14.2.3.3.2	Summary of Acute VVC by Study Visit, mITT Population
14.2.3.4.1	Summary of Culture Results by Study Visit, ITT Population
14.2.3.4.2	Summary of Culture Results by Study Visit, mITT Population

14.2.3.5.1	Summary of Signs and Symptoms Composite Score by Study Visit, ITT Population
14.2.3.5.2	Summary of Signs and Symptoms Composite Score by Study Visit, mITT Population
14.2.3.6.1	Summary of Signs by Study Visit, ITT Population
14.2.3.6.2	Summary of Signs by Study Visit, mITT Population
14.2.3.7.1	Summary of Symptoms by Study Visit, ITT Population
14.2.3.7.2	Summary of Symptoms by Study Visit, mITT Population
14.2.3.8.1	Proportion of Subjects with At Least One Culture-Verified Acute VVC Episode from Week 24 Through Week 48, ITT Population
14.2.3.8.2	Proportion of Subjects with At Least One Culture-Verified Acute VVC Episode from Week 24 Through Week 48, mITT Population
14.2.3.9.1	Proportion of Subjects with At Least One Culture-Verified Acute VVC Episode During Post Randomization Through Week 12, ITT Population
14.2.3.9.2	Proportion of Subjects with At Least One Culture-Verified Acute VVC Episode During Post Randomization Through Week 12, mITT Population
14.2.3.10.1	Proportion of Subjects with At Least One Culture-Verified Acute VVC Episode During Post Randomization Through Week 36, ITT Population
14.2.3.10.2	Proportion of Subjects with At Least One Culture-Verified Acute VVC Episode During Post Randomization Through Week 36, mITT Population
14.2.3.11.1	Proportion of Subjects with At Least One Signs and Symptoms Score ≥ 3 During the Maintenance Phase, ITT Population
14.2.3.11.2	Proportion of Subjects with At Least One Signs and Symptoms Score ≥ 3 During the Maintenance Phase, mITT Population
14.2.3.12.1	Summary of Number of Culture Confirmed Episodes During the Maintenance Phase, ITT Population
14.2.3.12.2	Summary of Number of Culture Confirmed Episodes During the Maintenance Phase, mITT Population
14.2.3.13.1	Summary of Number of Times Subject was Treated with a Known Treatment for VVC During the Maintenance Phase, ITT Population
14.2.3.13.2	Summary of Number of Times Subject was Treated with a Known Treatment for VVC During the Maintenance Phase, mITT Population
Safety	
14.3.1.1	Overall Summary of Adverse Events
14.3.1.2.1	Treatment-Emergent Adverse Events by System Organ Classification, Preferred Term, and Greatest Severity, Safety Population
14.3.1.2.2	Event Counts of Treatment-Emergent Adverse Events by System Organ Classification, Preferred Term, and Severity, Safety Population
14.3.1.3	Treatment-Emergent Adverse Events by System Organ Classification and Preferred Term, Safety Population

14.3.1.4	Treatment-Emergent Serious Adverse Events by System Organ Classification and Preferred Term, Safety Population
14.3.1.5	Treatment-Emergent Adverse Events Related to IMP by System Organ Classification and Preferred Term, Safety Population
14.3.1.6	Treatment-Emergent Adverse Events Related to IMP as evaluated by Mycovia by System Organ Classification and Preferred Term, Safety Population
14.3.1.7	Treatment-Emergent Adverse Events Leading to Discontinuation of IMP by System Organ Classification and Preferred Term, Safety Population
14.3.4.1.1	Summary of Hematology Results and Change from Baseline by Visit, Safety Population
14.3.4.1.2	Summary of Treatment-Emergent Abnormal Hematology by Visit, Safety Population
14.3.4.2.1	Summary of Serum Chemistry Results and Change from Baseline by Visit, Safety Population
14.3.4.2.2	Summary of Treatment-Emergent Abnormal Serum Chemistry by Visit, Safety Population
14.3.4.3.1	Summary of Urinalysis by Visit, Safety Population
14.3.4.3.2	Summary of Treatment-Emergent Abnormal Urinalysis by Visit, Safety Population
14.3.4.4.1	Summary of Subjects Experiencing At least One Treatment-Emergent Graded Laboratory Toxicity by Visit, Safety Population
14.3.4.4.2	Shifts from Baseline for Graded Laboratory Toxicities by Visit, Safety Population
14.3.4.4.3	Summary of Subjects with Grade 3 or 4 Treatment-Emergent Laboratory Toxicities by Visit, Safety Population
14.3.5.1.1	Summary of ECG Results and Change from Baseline by Visit, Safety Population
14.3.5.1.2	Proportion of Subjects with Abnormal ECG Interpretations by Visit, Safety Population
14.3.5.2	Summary of Vital Signs and Change from Baseline, Safety Population
14.3.5.3	Concomitant Medications, Safety Population

Figures

14.1.3.3.2	VT-1161 Mean Plasma Concentration by Visit, ITT Population Randomized to VT-1161
14.2.1.2	Proportion of Subjects with One or More Culture-Verified Acute VVC Episodes During the Maintenance Phase by Treatment Group, ITT Population
14.2.2.1.2	Kaplan-Meier Time to First Recurrence of Culture-Verified Acute VVC by Treatment Group, ITT Population
14.2.2.2.2	Proportion of Subjects with At Least One Positive Culture During the Maintenance Phase by Treatment Group, ITT Population
14.2.2.3.2	Proportion of Subjects with At Least One Culture-Verified Acute VVC Episodes Post Randomization Through Week 24 by Treatment Group, ITT Population

Data Listings

16.2.1	Early Termination/Study Completion
16.2.2	Protocol Deviations
16.2.3.1	Study Populations
16.2.3.2	Inclusion/Exclusion Criteria
16.2.4.1	Demographics
16.2.4.2	Medical and Surgical History
16.2.4.3.1	Recurrent VVC History
16.2.4.3.2	Recurrent VVC History Questionnaire – US Only
16.2.4.4	Substance Use
16.2.5.1.1	Study Drug Administration - Fluconazole
16.2.5.1.2	IMP Administration – VT-1161 or Placebo
16.2.5.1.3	Study Drug Exposure and Compliance
16.2.5.1.4	VT-1161 Plasma Concentration
16.2.5.2.1	Prior and Concomitant Medications
16.2.5.2.2	Concomitant Therapies and Procedures
16.2.6.1	Primary Efficacy and Key Secondary Efficacy Endpoints
16.2.6.2	Clinical Signs and Symptoms
16.2.6.3	KOH/Gram Results
16.2.6.4	Culture Assessments
16.2.6.5	KOH/Gram Result, Culture Result, Total Signs and Symptoms, and Culture-Verified Acute VVC Infection
16.2.6.6.1	SF-36 Patient Reported Outcome Survey
16.2.6.6.2	SF-36 MCS, PCS, Total Score, and Domain Scores
16.2.6.7	EQ-5D-3L/EQ-5D-Y Patient Reported Outcome Survey
16.2.6.8	Work Productivity and Activity Impairment Questionnaire
16.2.6.9	Patient Health Questionnaire - 9
16.2.7.1	Adverse Events
16.2.7.2.1	Serious Adverse Events
16.2.7.2.2	Details for Serious Adverse Events
16.2.7.3	Adverse Events Leading to Discontinuation
16.2.8.1.1	Laboratory Tests – Hematology
16.2.8.1.2	Laboratory Tests – Serum Chemistry
16.2.8.1.3	Laboratory Tests – Urinalysis
16.2.8.1.4	Laboratory Tests – Immunology
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16.2.8.1.6	Pregnancy Tests

16.2.8.2 Vital Signs
16.2.8.3 Physical Examination
16.2.8.4 ECG
16.2.8.5 Comments

13. APPENDIX 1: SCHEDULE OF EVENTS/STUDY VISITS

Activities	Screening Day -14 (±2 days)	Baseline (Day 1)	Day 14 (±2 days)	Week 6 (±7 days)	Week 12 (±14 days) EOT	Week 18 (±14 days)	Week 24 (± 14 days)	Week 30 (± 14 days)	Week 36 (± 14 days)	Week 42 (± 14 days)	Week 48 (± 14 days) EOS	Unscheduled Visit[j]
Sign Informed Consent and/ or Assent Form	X											
Inclusion/ Exclusion Criteria	X	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
Patient Reported Outcome Surveys[b]	X						X				X	X
RVVC History Questionnaire (US Only)	X											
Body Height and Weight	X				X[c]		X[c]				X[c]	
Vital Signs[d]	X	X	X	X	X	X	X	X	X	X	X	X
Physical and Vaginal Examination	X	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]
Clinical Signs & Symptoms of Vulvovaginitis	X	X	X	X	X	X	X	X	X	X	X	X
Local KOH Wet Mount or Gram Stain	X											X
Central Vaginal Fungal Culture	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X	X	X		X		X				X	
PK Samples[f]		X	X		X		X		X		X	X
Clinical Laboratory Samples[g]	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X		X		X		X		X	
Hematology (CBC with differential)	X	X	X		X		X		X		X	
HIV Ab, HBsAg, anti-HCV	X											
Central Serum Pregnancy Test[h] (WOCBP)	X	X			X		X				X	
Local Urine Pregnancy Test[h] (WOCBP)	X	X	X	X	X	X	X	X	X	X	X	X
Administer Fluconazole	X											
Randomization		X										
Administer and/or Review IMP[i]		X	X	X	X							

Abbreviations noted above - AEs: adverse events; CBC, complete blood count; ECG: electrocardiogram; EOS: End of Study; HBsAg: Hepatitis B surface antigen; HCV: Hepatitis C virus; HIV: human immunodeficiency virus; IMP, investigational medicinal product; KOH: potassium hydroxide prep; PK: pharmacokinetic; 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. SF-36, EQ-5D-3L or EQ-5D-Y (for ages 12 to 17), WPAI:SHP, and PHQ-9 patient reported outcome surveys.
c. Weight only
d. Vital signs include sitting heart rate, blood pressure, temperature, and respiratory rate.
e. Limited Physical Examination, i.e. vaginal speculum examination plus a symptom-directed physical examination.
f. PK Samples should be collected before the weekly dosing of study drug (placebo/VT-1161).
g. 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 for all 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.
h. For WOCBP, a local lab urine pregnancy test will be obtained at every study visit. A central lab serum pregnancy test will also be performed at Screening, Baseline, and Weeks 12, 24, and 48.
i. 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. Remind subject to bring IMP to each visit to ensure compliance.
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.