PRS COVER PAGE for PROTOCOL

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)

DATE: 17 January 2019

CLINICALTRIALS.GOV ID: NCT03840616

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

Study Number: VMT-VT-1161-CL-017

Version: 2

Date of Issue: 17 January 2019

Mycovia Pharmaceuticals, Inc
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PROTOCOL SIGNATURE PAGE

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

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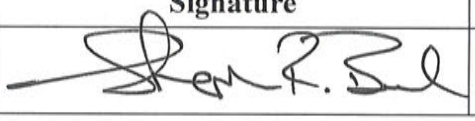
Signature of approval for protocol:

Name	Signature	Date
STEPHEN R. BRAND		17 JAN 2019

This study is to be performed in accordance with Good Clinical Practice, the ethical principles that have their origin in the Declaration of Helsinki, Title 21 of the Code of Federal Regulations, Parts 11 (Electronic Records; Electronic Signatures), 50 (Protection of Human Subjects), 54 (Financial Disclosure by Clinical Investigators), 56 (Institutional Review Boards), and 312 (Investigational New Drug Application), and International Conference on Harmonisation E6 (Guideline for Good Clinical Practice).

Study Sponsor: Mycovia Pharmaceuticals, Inc.
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Sponsor Contact: Stephen Brand, Ph.D.
Senior VP of Clinical Development
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Medical Responsible: Claude Hughes, M.D., Ph.D.
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Investigator's Statement

I have reviewed the protocol VMT-VT-1161-CL-017 entitled "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" and agree that it contains all the information necessary to conduct the study as required. I will conduct the study in accordance with the principles of International Conference on Harmonisation, Good Clinical Practice, and the Declaration of Helsinki.

I will maintain as confidential all written and verbal information provided to me by the Sponsor, including but not limited to, the protocol, case report forms, Investigational Brochure, material supplied at investigator meetings, minutes of teleconferences, etc. I agree that such material will only be provided as necessary to site personnel involved in the conduct of the study, the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), regulatory authorities, or agencies as required by local law.

I will obtain written informed consent or assent (for those ages 12-17) from each prospective study subject or each prospective study subject's legal representative prior to conducting any protocol-specified procedures. The consent form used will have the approval of the IRB/IEC.

I will maintain adequate source documents and record all observations, treatments, and procedures pertinent to study subjects in their medical records. I will accurately complete the case report forms supplied by the Sponsor in a timely manner. I will ensure that my facilities and records are available for inspection by representatives of the Sponsor, the IRB/IEC, or other applicable regulatory authorities. I will ensure that my staff and I are available to resolve queries and meet with representatives of the Sponsor during regularly scheduled monitoring visits.

I will notify the Sponsor within 24 hours of any serious adverse events. Following this notification, a written report describing the serious adverse event will be provided to the Sponsor within 1 business day following the initial notification.

I acknowledge that I am responsible for the overall study conduct, and I agree to personally conduct and/or supervise the study. I will ensure that all associates, colleagues, and employees assisting in the conduct of the study, are informed and trained as necessary about their obligations and that there are adequate mechanisms in place for the site staff to receive the appropriate information throughout the study.

_____
Name

_____ _____
Signature Date

PROTOCOL SYNOPSIS

Title of Study: 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

Protocol Number: VMT-VT-1161-CL-017

Interim Analysis: No

Investigational Medicinal Product: VT-1161 capsules

Non-Investigational Medicinal Product: Fluconazole tablets

Planned Number of Sites: Approximately 45 U.S.

Planned Number of Subjects: 360 screened; 180 randomized

Phase of Development: 3

Introduction:
VT-1161 is an orally-available inhibitor of fungal CYP51 that has shown high potency and selectivity in *in vitro* studies. VT-1161 blocks the production of ergosterol, an essential component of the fungal cell membrane, which is critical to fungal growth. *In vitro* and *in vivo* pharmacology studies have demonstrated that VT-1161 is highly active against *Candida albicans*, including fluconazole-resistant *C. albicans*, and non-albicans *Candida* species that cause vulvovaginal candidiasis (VVC). VT-1161 is highly selective for fungal CYP51 relative to off-target human CYP enzymes, and data to date suggest that it may avoid the side-effect profile that limits the use of commonly prescribed azole antifungal agents.

Oral VT-1161 has been evaluated in Phase 1 and 2 studies and shown to be safe, well tolerated, and highly effective in the treatment of vulvovaginal infections caused by *Candida* species. For example, in a Phase 2b study in subjects with recurrent VVC (RVVC), subjects in the 12-week VT-1161 treatment group (150 mg VT-1161 once daily for 7 days followed by 150 mg VT-1161 once weekly for 11 weeks) showed a 4.8% recurrence rate through Week 48 compared with a 52% recurrence rate in the placebo group in the intent-to-treat analysis.

RVVC, defined as 3 or more acute VVC episodes over a 12-month period, is experienced by 5 to 7 million women each year in the US. *Candida albicans* is the leading cause of recurrent vulvovaginal yeast infections in the United States. However, there has been an increasing trend in the number of vaginal yeast infections attributable to non-albicans species such as C. *glabrata* and C. *tropicalis*. In addition to the use of topical products to treat VVC, the majority of the women visiting healthcare professionals receive fluconazole for the treatment of each acute episode. A smaller percentage are prescribed a fluconazole maintenance regimen although fluconazole is not currently approved for the treatment of RVVC. Since some of the C. *albicans* and the majority of non-albicans isolates are resistant to fluconazole, the management of RVVC has become even more challenging.

In both nonclinical studies and clinical trials conducted to date, VT-1161 has demonstrated a favorable safety and tolerability profile, with no discernable adverse effect on liver function. In reproductive toxicity studies in pregnant rats or rabbits, VT-1161 was not teratogenic at any exposure studied. In a recent CYP3A4 drug-drug interaction study utilizing midazolam as the substrate, no clinically significant inhibition and only weak induction of midazolam metabolism was observed. These data are favorable when compared to other oral antifungal agents such as fluconazole. This study is to evaluate the efficacy and safety of VT-1161 compared to fluconazole in treating acute VVC infections in RVVC subjects.

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 VVC episode in RVVC subjects.

Secondary:

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

Methodology:

Study Design:

This is a Phase 3, multicenter, randomized, double-blind study to evaluate the efficacy and safety of VT-1161 oral capsules versus fluconazole in the treatment of acute vulvovaginal candidiasis episodes in subjects with recurrent vulvovaginal candidiasis. In addition, the study will evaluate the efficacy of oral VT-1161 compared to placebo in the prevention of RVVC through Week 50 after treating the acute episodes of VVC with treatment of VT-1161 or fluconazole. Approximately 180 subjects will be randomized, 120 subjects in the VT-1161 arm and 60 subjects in the fluconazole and placebo arm.

Subjects must have a history of RVVC, defined as at least 3 episodes of acute VVC in the past 12 months, as described below:

- Subjects must have an acute VVC episode at the time of Screening, with a documented positive potassium hydroxide (KOH) performed at the investigative site
- Subjects must also have had 2 or more additional episodes of acute VVC in the past 12 months, with at least 1 of the episodes documented by a positive confirmatory laboratory test (i.e., culture, PCR, Affirm test, KOH test, a documented Papanicolaou (Pap) test, or other approved diagnostic tests)

Subjects must also have an acute VVC episode at Screening, defined as a total signs and symptoms score of ≥3.

The study consists of two Phases:

1) an Induction Phase for the treatment of the acute VVC episode in which subjects will be randomized to receive one of the following:

- 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.

2) a Maintenance Phase in which subjects initially randomized to receive VT-1161 in the Induction Phase will receive 150 mg VT-1161 (1 x 150 mg capsule) weekly for 11 weeks and will then enter a 37-week follow-up period. Subjects randomized to receive over-encapsulated fluconazole in the Induction Phase will receive placebo weekly for 11 weeks and will then enter a 37-week follow-up period.

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, weight and height, 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 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 ≥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 to enter the Induction Phase.

At Screening (Day 1), subjects presenting with an acute infection and meeting all study eligibility criteria will enter the Induction Phase where they will be randomized 2:1 ratio to receive 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 infection has resolved (defined by a signs and symptoms score of <3). If the acute VVC has not resolved, the subject will be considered a screen failure and encouraged to see their physician for follow-up care.

All subjects in which the acute VVC infection has resolved will continue into a Maintenance Phase. Subjects initially randomized to receive VT-1161 in the Induction Phase will receive 150 mg VT-1161 (1 x 150 mg capsule) weekly for 11 weeks and will then enter a 37-week follow-up period. Whereas subjects randomized to receive over-encapsulated fluconazole in the Induction Phase will receive placebo weekly for 11 weeks and will then enter a 37-week follow-up period.

Subject's 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. Subject's Day 14 is defined as the first day of weekly dosing of IMP administration.

Study Duration:

The study duration is expected to be approximately 18 months from screening of the first subject until last follow-up of the last subject.

Subject Participation:

The duration of individual subject participation will be approximately 50 weeks. See Table 1 for the Schedule of Assessments and Procedures which will be performed. After Screening, subjects will return to the clinic on Day 14 (±2 days), the start of the Maintenance Phase. Subjects will then have visits on Weeks 8 (±7 days), 14 (±14 days) (end of treatment [EOT]), 20 (±14 days), 26 (±14 days), 32 (±14 days), 38 (±14 days), 44 (±14 days) and 50 (±14 days) (end of study [EOS]). Subjects who return to the clinic for a recurrent acute VVC episode should be evaluated as per the unscheduled visit noted in the Schedule of Assessment and Procedures.

Scoring of Vulvovaginal Signs and Symptoms:

Vulvovaginal signs and symptoms will be evaluated at Screening and at each subsequent study visit. Each of the following vulvovaginal signs and symptoms will be scored and the individual scores combined, for a maximum score of 18 using the following scale:

a. Signs: erythema, edema, and excoriation
b. Symptoms: itching, burning, and irritation

Scoring Scale: Each score should be graded on a scale of 0 to 3 as follows:

0 = none (complete absence of any sign or symptom)
1 = mild (slight)
2 = moderate (present)
3 = severe (marked, intense)

Mycology Assessment:

A local mycological assessment using KOH wet mount followed by microscopy will be evaluated at the Screening (Day 1) and at any study visit where a recurrent acute VVC episode is suspected. In addition, a vaginal swab for culture testing will be obtained and sent to the central mycology laboratory at the Screening and each subsequent study visit.

Plasma Pharmacokinetics:

Blood samples for assay of VT-1161 plasma concentrations will be collected from subjects at Day 14, Week 14 and Week 50 visits.

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.

Safety:

Subject safety will be monitored by collection of adverse events (AEs), changes in vital signs, physical and vaginal exam parameters, ECGs, and safety laboratory parameters, including pregnancy tests for women of childbearing potential (WOCBP).

Concomitant Medications:

The following prescription and over-the-counter drug products are prohibited during the study and will be considered a protocol deviation:

1. Topical or oral antifungal drugs (with the exception of fluconazole when prescribed by the Investigator to treat a subject with a recurrent VVC episode. If subject fails to respond to fluconazole treatment, the Investigator may employ treatment options corresponding to the site's standard of care treatment to treat the infection upon consult with the Medical Monitor.)
2. Topical products applied to the vulva or vagina (e.g. antibiotic, antitrichomonal, corticosteroids, or anti-inflammatory agents).
3. Oral antibacterial or antitrichomonal agents for the treatment of bacterial vaginosis, trichomonas, or other concomitant urogenital infection unless prescribed by the Investigator.
4. Oral or injectable corticosteroid or immunosuppressive drugs for the duration of the study. Use of topical (no vulvar or vaginal steroids), inhaled, ophthalmic, or intraarticular and intralesional

steroids is permitted.

5. Drugs with a narrow therapeutic index that are metabolized by CYP3A4 and sensitive to induction of CYP3A4 (carbamazepine, cyclosporine, fentanyl, quinidine, sirolimus and tacrolimus).

Number of Subjects (Planned):

Approximately 180 randomized subjects are planned for this study. Assuming a 20% discontinuation rate for the duration of the study, approximately 144 subjects are expected to complete the study.

Criteria for Inclusion and Exclusion:

Criteria for Inclusion:

1. Subjects must be generally healthy, post-menarchal females 12 years of age and older as of Screening (Day 1).
2. Subjects must have a history of recurrent VVC as defined by three (3) or more episodes of acute VVC in the past 12 months, including the episode confirmed at Screening, with at least one episode (not including the current episode) documented by a positive culture, PCR, Affirm test, KOH test, or a documented Pap test in the prior 12 months revealing filamentous hyphae/pseudohyphae and/or budding yeast cells.
3. Subjects must have an acute VVC episode at Screening, defined as a total signs and symptoms score of ≥3 and a positive KOH wet mount preparation from a vaginal smear revealing filamentous hyphae/pseudohyphae and/or budding yeast cells.
4. Subjects must have a composite vulvovaginal signs and symptoms score of <3 at the Day 14 Visit.
5. Subjects must have a documented Pap test results at Screening or within the current standard of care guidelines for the appropriate age requirement, reported as either "negative for intraepithelial lesion or malignancy" or "ASCUS-atypical squamous cells of undetermined significance" (not applicable to subjects with a history of total hysterectomy).
6. Subjects must be suitable candidates for oral therapy and be able to swallow capsules intact.
7. Subjects must be willing and able to provide written informed consent or assent (for those ages 12-17) and authorization for use of protected health information.
8. Subjects must be willing and able to comply with protocol requirements, instructions, and protocol-stated restrictions and be likely to complete the study as planned.
9. Subjects of non-childbearing potential must meet the requirements defined below:
    a. Pre-menopausal with documentation of surgical sterilization (i.e., hysterectomy, bilateral tubal ligation, bilateral oophorectomy, or bilateral salpingectomy) at least 3 months prior to study entry.
    b. Post-menopausal defined as amenorrhea for at least 12 months following cessation of all exogenous hormonal treatments at Screening.
10. Subjects of childbearing potential (includes ages 12-17) must use 1 of the following methods of contraception during the study through Week 50:

    OPTION 1 - Highly effective methods that can be used alone:

    1. Copper intrauterine device used continuously and successfully for at least 90 days prior to first dose of study drug[a]
    2. Levonorgestrel-releasing intrauterine system used successfully for at least 90 days prior to first dose of study drug[a]
    3. Progestin implant used successfully for at least 90 days prior to first dose of study drug[a]

4. Monogamous with a vasectomized male partner (vasectomy performed at least 6 months prior to first dose of study drug)[a]
5. Abstinence[b]

OPTION 2 – Acceptable first and second barrier methods to be used in combination:

FIRST *(Hormonal Contraception)*[a]

1. Estrogen & progestin oral contraceptives, transdermal patch or vaginal ring used successfully for at least 90 days prior to first dose of study drug
2. Progestin only oral contraceptives or injection used successfully for at least 90 days prior to first dose of study drug

SECOND *(Barrier Method)*

1. Diaphragm (with spermicide)
2. Cervical cap (with spermicide)
3. Male condom (with or without spermicide)

In addition to OPTIONS 1 and 2, subjects of childbearing potential (includes ages 12-17) may also use 1 of the following methods of contraception after completing the Induction Phase on Study Day 14 through Week 50:

OPTION 3 (Day 14 – Week 50)[c] – Acceptable first and second barrier methods to be used in combination:

FIRST *(Barrier Method)*

1. Diaphragm (with spermicide)
2. Cervical cap (with spermicide)

SECOND *(Barrier Method)*

1. Male condom (with or without spermicide)

[a] Subjects who started using an intrauterine device or any of the hormonal contraceptive methods described above less than 3 months prior to the first dose of study medication must agree to use a double-barrier method (i.e., diaphragm plus spermicide or condom) through 3 months after start of the use of the IUD or hormonal contraceptive. Similarly, subjects that claim a monogamous relationship with a vasectomized male partner where the vasectomy was performed less than 6 months prior to the first dose of study medication, must agree to use a double-barrier method (i.e., diaphragm plus spermicide or condom) through 6 months after the date of the vasectomy.

[b] Sexual abstinence is defined as refraining from heterosexual intercourse during the entire study period and where this is the usual life style of the subject. Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not considered to be acceptable methods of contraception.

[c] Because of the teratogenic risk associated with repeat dosing of fluconazole, OPTION 3 contraceptive methods cannot be used during Screening and the Induction Phase of the study [from Screening (Day 1) until Day 14 of the study].

Criteria for Exclusion:

1. Subjects must not have the presence of concomitant vulvovaginitis caused by other pathogens (e.g., bacterial vaginosis, *Trichomonas vaginalis*, *Chlamydia trachomatis*, or *Neisseria gonorrhoeae*) at Screening (Day 1) visit.
2. Subjects must not have an active HPV infection as evidenced by visible condylomas on vulvovaginal examination at Screening (Day 1) visit.
3. Subjects must not have the presence or a history of another vaginal or vulvar condition(s) that in

the Investigator's opinion would confound the interpretation of clinical response.

4. Subjects must not have a history of cervical cancer.
5. Subjects must not use any systemic (e.g., oral or injectable) corticosteroid therapy during the study or within 30 days prior to Screening visit; nor use of topical vulvar or vaginal steroids during the study or within 7 days prior to Screening visit. However, use of topical (no vulvar or vaginal steroids), inhaled, ophthalmic, collunarium/nasal, intraarticular and intralesional steroids is permitted.
6. Subjects must not use any systemic (e.g., oral or injectable) or topical (applied to the vulva or vaginal area) antifungal, antibacterial, or antitrichomonal drugs for the treatment of bacterial vaginosis, trichomonas, or other concomitant urogenital infection during the study (unless prescribed by the Investigator) or within 7 days prior to Screening.
7. Subjects must not be using drugs with a narrow therapeutic index that are metabolized by CYP3A4 and sensitive to induction of CYP3A4 during the study (carbamazepine, cyclosporine, fentanyl, quinidine, sirolimus and tacrolimus).
8. Subjects must not use any vaginal estrogen replacement therapy, ospemifene, Vitamin E gel capsules (vaginally) or lubricants within 7 days prior to Screening.
9. Subjects must not have a condition that would require treatment during the study with concomitant topical (applied to vulva and vagina) or systemic antimicrobial therapy for any reason.
10. Subjects must not have received an immunosuppressive medication (e.g. cyclosporine, tacrolimus, methotrexate, 6-mercaptopurine, mycophenolate, etc.), or radiation therapy within 3 months prior to Screening or have a medical condition where it would be likely that the subject may need to use these therapies during the study.
11. Subjects must not have evidence of any clinically significant major organ disease or current clinically significant infection or any other conditions (with the exception of acute VVC) that may affect the clinical assessment of RVVC per investigator judgment.
12. Subjects must not have any comorbid condition that in the opinion of the Investigator would preclude the safe participation of the subject in the study or would prevent the subject from meeting the study requirements.
13. Subjects must not have any condition that in the opinion of the investigator could impact drug absorption (e.g. gastrectomy, Roux-en-Y gastric bypass surgery, gastric bands or staples, etc.), distribution, or elimination.
14. Subjects must not have poorly controlled diabetes mellitus (HbA1c ≥8.5% at Screening; performed only on known diabetics or subjects suspected to have diabetes by the investigative site).
15. Subjects must not have moderate or severe hepatic and/or renal disease (defined in Appendix B and Appendix C).
16. Subjects must not have a laboratory abnormality that in the opinion of the Investigator is likely to introduce additional risk to the subject or might interfere with data interpretation. The specific findings listed below are excluded at Day 1 (a single repeat laboratory evaluation is allowed for eligibility determination, except for HIV, HBsAg and antibodies to hepatitis C virus):
    a. Serum alanine aminotransferase (ALT) ≥2.0x the upper limit of normal (ULN) of the reference range.
    b. Serum aspartate aminotransferase (AST) ≥2.0x the ULN of the reference range.
    c. Serum total bilirubin ≥1.5x the ULN of the reference range, unless the elevation is consistent with Gilbert's Syndrome.
    d. Electrocardiographic QTc interval >470 msec as corrected by the Fridericia formula, or any clinically significant electrocardiographic abnormality.

e. Positive test for antibodies to human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or antibodies to hepatitis C virus.

17. Subjects of childbearing potential must not be pregnant (positive pregnancy test at Screening), lactating, or planning to become pregnant during the study period.
18. Subjects must not have planned surgery or other medical procedures that in the Investigator's opinion would impact compliance with the protocol.
19. Subjects must not have active substance abuse (e.g., drugs of any kind, including alcohol) or any other medical, psychiatric or social condition that in the Investigator's opinion would preclude compliance with the protocol.
20. Subjects must not have received VT-1161 study medication in a previous study.
21. Subjects must not have received any IMP in a clinical trial within 5 half-lives of that IMP prior to Screening (if unknown, 60 days prior to Screening).
22. Subjects must not have a known history of intolerance or hypersensitivity to azole antifungal drugs (e.g., fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole), or any excipients of the capsule formulation.

Induction Treatment Phase

Investigational Medicinal Product: VT-1161 150 mg capsules

Dose and Mode of Administration:

Oral administration of 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.

Oral administration of IMP within 30 minutes after ingestion of the subject's main meal of the day (as determined by the subject and kept consistent throughout the duration of the study). Approximately 240 mL (approx. 8oz) of water is to be consumed with each dose of IMP.

Placebo capsules matching the VT-1161 capsules will be administered on Day 1 (4 capsules) and Day 2 (3 capsules) to maintain study blind for those subjects randomized to the fluconazole treatment arm.

Investigational Medicinal Product: Fluconazole 150 mg tablets, over-encapsulated

Dose and Mode of Administration:

Oral administration of 3 sequential doses (every 72 hours) of fluconazole 150 mg starting on Day 1.

Oral administration of IMP within 30 minutes after ingestion of the subject's main meal of the day (as determined by the subject and kept consistent throughout the duration of the study). Approximately 240 mL (approx. 8oz) of water is to be consumed with each dose of IMP.

Placebo capsules matching the over-encapsulated fluconazole IMP will be administered on Day 1, 4 and 7 to maintain study blind for those subjects randomized to the VT-1161 treatment arm.

Maintenance Treatment Phase

Maintenance Phase Test Product: VT-1161 150 mg capsules

Dose and Mode of Administration:

Oral administration of VT-1161 within 30 minutes after ingestion of the subject's main meal of the day (as determined by the subject and kept consistent throughout the duration of the study). Approximately 240 mL (approx. 8oz) of water is to be consumed with each dose of IMP.

Starting on Day 14, VT-1161 150 mg (1 capsule) will be given once weekly for 11 weeks.

Duration of Administration: 11 weeks

Maintenance Phase Reference Product: Matching Placebo capsules

Dose and Mode of Administration:

Oral administration of placebo within 30 minutes after ingestion of the subject's main meal of the day (as determined by the subject and kept consistent throughout the duration of the study). Approximately 240 mL (approx. 8oz) of water is to be consumed with each dose.

Starting on Day 14, placebo (1 capsule) will be given once weekly for 11 weeks.

Duration of Administration: 11 weeks

Study Populations:

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

Safety Population: All randomized subjects who received at least 1 dose of study drug.

Per Protocol Population (PP): All randomized subjects who had the following:

- Had no deviations to inclusion/exclusion criteria that could impact treatment outcome.
- Were compliant with the assigned study treatment, defined as ≥80% compliance during the Induction Phase and ≥50% compliance 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.

Modified ITT: All enrolled subjects who had the following:

- Positive KOH at Screening.
- Positive culture at Screening.
- Negative culture at Day 14.

Criteria for Evaluation:

Efficacy:

Clinical and mycological assessments will be conducted as outlined in Table 1. Schedule of Assessments and Procedures.

All efficacy analyses will be performed on the ITT, PP, and mITT Populations.

The primary efficacy outcome measure is the proportion of subjects with one or more culture-verified acute VVC episodes (post-randomization through Week 50) in the ITT population, which will include the subjects who failed clearing their infection during the Induction Phase. 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.

The key secondary efficacy outcome measures include the following:

a. 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.
b. The proportion of subjects with at least one culture-verified acute VVC episode with signs and symptoms of ≥3 during the Maintenance Phase (post Day 14 through Week 50).
c. 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).
d. The proportion of subjects with at least one positive culture for *Candida* during the Maintenance Phase.

Safety:

All safety analyses will be performed on the Safety Population. AEs will be collected throughout the study. Physical and vaginal examination findings and vital signs will be recorded at Screening and throughout the study per Table 1. Schedule of Assessments and Procedures. ECGs and safety laboratory tests (hematology, chemistry, and urinalysis) will be obtained throughout the study. All concomitant medications taken during the period from 30 days prior to Screening through the Week 50 (EOS) visit will be recorded in the case report form (CRF). Pertinent and all major medical conditions will be recorded on the Medical History CRF.

Subjects who want to discontinue from the study should be encouraged to remain in the study for all remaining visits through Week 50 for safety and efficacy assessments. All subjects who discontinue early from the study should have all EOS procedures performed on the day of discontinuation.

Statistical Methods and Data Analysis:

A statistical analysis plan will be finalized before 50% of subjects are enrolled.

Efficacy Analysis:

The statistical objectives of this study will be:

1. To determine if there is a difference in the proportions of subjects with one or more episodes of culture-verified acute VVC in those receiving VT-1161 compared to those receiving placebo
2. To determine if there is a difference in the ability of VT-1161 and fluconazole to resolve acute episodes in subjects with RVVC.

A sample size of 82 subjects in the VT-1161 arm and 41 subjects in the fluconazole/placebo arm provides at least 90% power to detect a treatment difference between the VT-1161 treatment group and the fluconazole /placebo treatment group with a type 1 error rate of 0.05. Sample size calculation assumes 50% of the subjects in the placebo arm will have at least one culture-verified acute VVC episode post-randomization through Week 50. 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. The sample size calculation assumes that 90% of the subjects in the fluconazole arm will resolve their acute VVC infection by Day 14.

For the efficacy analyses, missing values for the investigator's assessment of clinical signs and symptoms or the culture result 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.

A chi-square test will be used to compare the proportion of subjects with one or more culture-verified acute VVC in those receiving VT-1161 compared to those receiving fluconazole and placebo. The proportion of subjects who have cleared their infection at Day 14 in those receiving VT-1161 will be evaluated for non-inferiority versus those receiving fluconazole utilizing a non-inferiority margin of 15%.

Safety Analysis:

AEs will be coded using the Medical Dictionary for Regulatory Activities® dictionary. The number and percentage of subjects reporting treatment-emergent AEs will be tabulated by system organ class, preferred term, and greatest severity with a breakdown by treatment group. Mean changes from pre-treatment in vital signs, ECG, and clinical laboratory variables will be summarized by treatment group.

Pharmacokinetics:

No formal statistical hypothesis testing related to pharmacokinetics will be conducted. VT-1161 concentrations will be presented by visit with descriptive statistics. The pharmacokinetic data will be used in a cross-population pharmacokinetic analysis that will be presented in a separate report.

Blood samples for assay of VT-1161 plasma concentrations will be collected from subjects prior to IMP on Day 14 and Week 14 and at Week 50. Intense sampling will be obtained only from consenting subjects at participating sites on Day 1 and Day 2 (predose and 1, 2, 4, and 8 hours after dosing, with ±10-minute window per timepoint).

Table 1. Schedule of Assessments and Procedures

Activities	Screening (Day 1)	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 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 and 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: 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, AST, ALT, alkaline phosphatase, total bilirubin, conjugated bilirubin, albumin, total protein, total carbon dioxide, glucose, sodium, potassium, chloride, calcium, and phosphorus, creatine phosphokinase [CK], cholesterol and triglycerides). Testing for HbA1c is performed only in known or suspected diabetic subjects at Screening. Cultures to test 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 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 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.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition or Term
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
CK	creatine phosphokinase
C_{max}	maximum plasma concentration
CRF	case report form
CYP51	lanosterol demethylase
DDI	drug-drug interaction
DMID	Division of Microbiology and Infectious Diseases
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study
FDA	Food and Drug Administration
GCP	good clinical practice
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
IC_{50}	half maximal inhibitory concentration
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IRB	institutional review board
ITT	intent-to-treat
IWRS	interactive web response system
KOH	potassium hydroxide
MedDRA	Medical Dictionary for Regulatory Activities
MIC_{50}	minimum inhibitory concentration
NOAEL	no-observed-adverse-effect-level
OM	Onychomycosis
Pap	Papanicolaou
PK	Pharmacokinetic
PKE	pharmacokinetic evaluation
PP	per protocol
QTc	duration of the QT interval adjusted for heart rate (Fridericia correction)
RVVC	recurrent vulvovaginal candidiasis

Abbreviation	Definition or Term
SAE	serious adverse event
SAP	statistical analysis plan
TEAE	treatment-emergent adverse event
T_{max}	time to reach maximum plasma concentration
TOC	test of cure
ULN	upper limit of normal
VVC	vulvovaginal candidiasis
WOCBP	women of childbearing potential

1 INTRODUCTION

Lanosterol demethylase (CYP51), an enzyme essential for fungal growth, catalyzes an early step in the biosynthetic pathway of ergosterol, a sterol required for fungal cell membrane formation and integrity (Yoshida, 1988). Inhibition of CYP51 results in the accumulation of 14-methylated sterols, some of which are toxic to the fungus. CYP51 is the molecular target of the class of drugs referred to as 'azole antifungals'. All currently approved azole drugs contain either an imidazole or triazole ring system that binds tightly to the catalytic heme-iron of fungal CYP51 as well as to the heme-iron of many off-target mammalian cytochrome P450 enzymes. This inherent lack of selectivity is responsible for many of the side effects associated with the azole antifungals. For example, the potent inhibition of one or more human cytochrome P450 metabolizing enzymes found in the liver (e.g. CYP3A4, CYP2C9, CYP2C19) or in the adrenal and sex organs (e.g. CYP19, CYP17, CYP21), is the basis for azole drug-drug interactions (Bates and Yu, 2003) and reproductive warnings (Zarn et al., 2003), respectively. Additional azole class toxicities that are less well understood but may be related to off-target protein interactions include hepatic toxicities, skin photosensitivity, and vision impairment. In the acute care setting, these dose-limiting side effects prevent attainment of plasma drug levels that might reduce the longstanding 40% mortality rate attributed to invasive fungal infections. The safety profile of the class similarly limits its use for chronic treatment of non-life-threatening fungal infections, such as recurrent vulvovaginal candidiasis (RVVC) and onychomycosis (OM). A safer antifungal drug would also improve treatment options for infections seen in otherwise healthy individuals, such as RVVC and OM, which require protracted treatment in a patient population where significant side-effect risks are unacceptable.

1.1 Background Information

Mucosal candidiasis, also known as thrush, describes a group of yeast-like fungal infections that involve the mucous membranes including the mouth, urinary tract and genitals, notably the vagina and surrounding skin in women. Infection is typically caused by *Candida albicans*, however more rare and difficult-to-treat *Candida* strains such as *C. glabrata* are becoming more prevalent. Mucosal candidiasis occurs more frequently in immunocompromised patients but may also arise in immunocompetent individuals.

1.1.1 Vulvovaginal Candidiasis

1.1.1.1 Epidemiology

Symptoms of vulvovaginitis (inflammation of the vagina and vulva) are common and are among of the most frequent reasons for women's visits to physicians. Vulvovaginitis is associated with considerable morbidity including genital discomfort, decrease in sexual pleasure, loss of productivity, and psychological distress (Eschenbach, 2004). There are several etiologies for vulvovaginitis; candidiasis being the second most common after bacterial vaginitis. Vulvovaginal candidiasis is a common disorder, with nearly 75% of all adult women having had at least one "yeast infection" in their lifetime. Approximately half of these women experience a recurrence, with 5 to 8% developing recurrent VVC, defined as 3 or more episodes in one year (Sobel, 2016). Estrogen increases the glycogen concentration of the vaginal lining; glycogen is a substrate on which *C. albicans* thrives. As estrogen levels are significantly lower in both pre-menarchal and post-menopausal females, the incidence of VVC is lower in these populations. Vulvovaginal candidiasis is most common in women aged 25 to 34 years (Foxman et al., 2013).

1.1.1.2 Pathophysiology

Vulvovaginal candidiasis occurs when there is an overgrowth of the normal yeast in the vagina. Most cases (85% - 95%) are caused by *C. albicans*, followed by *C. glabrata*, and infrequently by *C. parapsilosis*, *C. tropicalis*, and *C. krusei*. Vulvovaginitis caused by non-albicans *Candida* species, in particular *C. glabrata*, is clinically indistinguishable from *C. albicans* VVC but is more resistant to current treatments.

Candida organisms gain access to the lumen and secretions of the vagina primarily from the adjacent perianal region. Normal anti-*Candida* defense mechanisms allow for long-term persistence of *Candida* as commensal organisms in the vagina without signs or symptoms of vaginitis. Factors predisposing to VVC versus asymptomatic colonization include those attributed to the health (immunosuppression, use of antibacterial agents, pregnancy, uncontrolled diabetes mellitus) and behavior (frequent intercourse, orogenital sexual activity, use of oral contraceptives or estrogen-based hormonal replacement therapy) of the host. Other dermatologic conditions such as psoriasis, lichen planus, and lichen sclerosus also predispose women to VVC (Goncalves et al., 2016).

1.1.1.3 Presentation and Diagnosis

The clinical array of signs and symptoms of VVC include genital pruritus associated with edema, an erythematous rash and excoriation of the vulva and surrounding skin, a burning sensation in the vagina and vulva, and a vaginal discharge. These symptoms may persist for days to weeks and

may also recur with each menstrual cycle. Women with VVC typically most commonly present with acute pruritus and a vaginal discharge, though neither is specific for candidiasis. The discharge may range from being watery to quite thick and "cottage-cheese-like". Common symptoms include vaginal soreness, irritation, vulvar burning, dyspareunia, and external dysuria. Physical examination typically reveals erythema and edema of the vulva with fissures and a pustulopapular rash, vaginal erythema, and a normal cervix. Symptoms often worsen the week prior to menses.

The diagnosis of VVC requires more than a history and physical examination as symptoms and signs, in particular pruritus, are often non-specific. Diagnosis is made by microscopic examination of a 10% potassium hydroxide (KOH) wet mount showing the presence of yeast cells and mycelia and the absence of both clue cells (pathognomonic of bacterial infection) and trichomonads. The vaginal pH is normal, approximately 4.0%. A vaginal culture should also be performed, particularly for women with negative microscopy, as up to 50% of patients with culture-positive VVC will have no findings on microscopy (Sobel, 2007); additionally, a culture will precisely identify the organism. Papanicolaou (Pap) smears are also not reliable, typically positive in only a quarter of patients with VVC.

As up to 15% of asymptomatic women are colonized with *Candida* species and are thus culture positive, the final diagnosis of VVC requires a comprehensive assessment of clinical findings, microscopic examination, and vaginal culture.

1.1.1.4 Treatment and Outcome

In general, women who are asymptomatic carriers of *Candida* do not require treatment. Acute VVC in symptomatic women requires individualized treatment, the selected agent and duration of therapy being based on whether the VVC is categorized as either:

- Uncomplicated, defined as having all of the following characteristics: (mild or moderate in symptom severity, sporadic in frequency, *C. albicans* as the infecting organism, in non-pregnant women with normal immune function), or

- Complicated, defined as having any one or more of the following characteristics: severe in symptom severity, recurrent, a non-*C. albicans* organism as the infecting agent, abnormal immune function, or pregnant (Eschenbach, 2004).

Women with uncomplicated VVC can be treated with single-dose or short-course treatments, while those with complicated VVC require longer-term therapy, at least 5 to 7 days and possibly

maintenance therapy up to 6 months (Sobel et al., 2004). Pregnant women, who are at higher risk of developing VVC, can only be treated with topical agents because of the potential teratogenic effects of azoles when administered systemically. Topical agents are limited by local side effects, especially burning, and are messy to apply; therefore, most patients prefer the oral regimens. However, the systemically administered azoles listed in Table 2 are characterized by systemic toxicities and drug-drug-interactions (DDIs) and have poor activity against *C. glabrata* and fluconazole resistant C. *albicans*.

Table 2. Oral Agents Commonly Used to Treat VVC

Agent	Formulation	Dose and Schedule
Fluconazole (Diflucan®)	150 mg tablet (Rx)	Single dose
Ketoconazole (Nizoral®)	200 mg tablet (Rx)	2 tablets q.d. x5d
Itraconazole (Sporanox®)	100 mg tablet (Rx)	2 tablets q.d. x3d

Abbreviations: mg = milligrams; d = day; q.d. = once daily; Rx = prescription.

1.1.1.5 Recurrent, Resistant and Non-Albicans VVC

Up to 20% of women will develop recurrent, resistant, or complicated VVC. In a study that compared a 6-month maintenance weekly fluconazole regimen to placebo in patients with recurrent VVC, the time to recurrence increased from 4.0 to 10.2 months, and the cure rate at 12 months doubled versus placebo from 22% to 43% (Sobel et al., 2004). However, fewer than half of patients remained disease-free after discontinuation of fluconazole which highlights the unmet medical need for these patients.

The prevalence of infection with non-albicans species, in particular *C. glabrata*, is increasing, especially in patients who are immunosuppressed and/or are diabetics; *C. glabrata* is poorly sensitive to current azole antifungal agents.

1.2 VT-1161

VT-1161 is a novel oral antifungal agent with a lower affinity for heme-iron and a greater affinity for the fungal lanosterol 14 α-demethylase (CYP51) than the currently available azole drugs. As a result, VT-1161 more potently inhibits fungal CYP51 than current azoles and less potently inhibits host cytochrome P450 enzymes, resulting in greater cytochrome selectivity. These properties should translate to greater efficacy with an improved safety and tolerability profile.

VT-1161 is being developed for the treatment of patients with mucosal or superficial fungal infections. It is formulated with standard excipients known to be chemically stable when combined with VT-1161 into tablets or capsules for the investigational drug product.

A detailed description of the non-clinical binding and inhibition, metabolism, microbiology, toxicology, safety pharmacology, Phase 1 clinical studies in which 72 subjects were exposed to VT-1161 and Phase 2a proof-of-concept studies, in which 78 subjects were exposed to VT 1161 can be found in the VT-1161 Investigational Brochure. In the Phase 2b studies, 378 subjects were exposed to VT-1161. These studies are summarized below. The following sections provide data from non-clinical, Phase 1 and Phase 2 clinical trials supporting the use of VT-1161 for patients with RVVC.

1.2.1 Non-Clinical Pharmacology

1.2.1.1 Binding and Inhibition

In vitro pharmacology studies demonstrated that VT-1161 is a potent inhibitor of fungal CYP51 and binds more than 2200-fold more tightly to fungal CYP51 than to human CYP51. VT-1161 is also highly selective for fungal CYP51 versus key human cytochrome P450 enzymes, non-cytochrome metalloenzymes, and a broad panel of receptors, ion channels, and transporters.

1.2.1.2 Metabolism

VT-1161 was not significantly metabolized when incubated with mouse, rat, dog or human hepatocytes. Only 1 possible metabolite consistent with hydroxylation and glucuronidation of VT-1161 was detected in dog hepatocytes. No additional metabolites were detected in any of the 4 species.

1.2.1.3 Microbiology

VT-1161 was tested against a broad range of *Candida* clinical isolates and showed potent activity (

Table 3). It was also active against dermatophytes, including *Trichophyton rubrum*, *T. mentagrophytes*, and *T. tonsurans*.

Table 3. VT-1161 Antifungal MIC_{50} or Range (µg/mL)

Fungus (# of clinical isolates)	VT-1161	Comparator	
C. albicans (N=10)	≤ 0.03	Fluconazole	≤ 0.125
C. glabrata (N=10)	0.25		4
C. parapsilosis (N=10)	≤0.03		0.125
C. guilliermondii (N=3)	0.125-0.25		2-8
T. mentagrophytes (N=12)	0.25	Itraconazole	0.06
T. rubrum (N=41)	0.03		≤ 0.03
T. tonsurans (N=5)	0.06-0.5		≤0.03-0.06

Abbreviations: *C.* = *Candida*; *T.* = *Trichophyton*; MIC_{50} = minimum inhibitory concentration for 50% of isolates; µg = microgram; mL = milliliter; N = number (of clinical isolates).

In the Phase 2b RVVC study (VMT-VT-1161-CL-006), 413 clinical isolates were collected from subjects at screening visits until the end of the study. The minimum inhibitory concentration (MIC) ranges for VT-1161 and fluconazole for the isolates collected were; <0.0005 – >0.5 µg/ml and <0.06-32 µg/ml, respectively. The MIC_{50} values for VT-1161 and fluconazole were 0.004 µg/ml and 0.125 µg/ml, respectively, and the MIC_{90} values for VT-1161 and fluconazole were 0.06 µg/ml and 4 µg/ml, respectively. These data further demonstrated that VT-1161 has potent *in vitro* activity against the *Candida* strains obtained from clinical strains. For all tested isolates, VT-1161 demonstrated MIC_{50} and MIC_{90} that were 5 dilutions lower than those demonstrated by fluconazole.

1.2.1.4 Activity in Animal Models of VVC

VT-1161 was evaluated as an oral treatment of vaginal candidiasis (*C. albicans*) in a murine model (Garvey et al., 2012). Three days after infection, VT-1161 was dosed orally once daily at 4, 10, or 25 mg/kg daily for 4 days. Fungal burden measured in vaginal lavage fluid was highly significantly suppressed ($p < 0.0002$) compared to vehicle-treated controls at all doses and when measured 1 or 4 days after treatment ended. Plasma and vaginal tissue levels of the lowest dose of VT-1161 indicated that levels as low as 1 µg/mL resulted in this high degree of efficacy.

1.2.1.5 Pharmacokinetics

VT-1161 formulated as a suspension in carboxymethylcellulose was well absorbed and exhibited approximately dose linear pharmacokinetics (PK) and a long plasma half-life in both rats and dogs.

There was no evidence of an effect of gender on the PK of VT-1161 in either rats or dogs. VT-1161 accumulated during repeat-dosing in rats and dogs as expected based on the long half-life. VT-1161 was widely distributed into tissues and was mostly excreted in bile and feces in the rat. In vitro plasma protein binding of VT-1161 is high with approximately 99.5% binding to rat, dog and human plasma and slightly lower binding in mice (97.6%). The absolute oral bioavailability of the capsule formulation used in Phase 1 studies administered to dogs was approximately 40% in the fasted state and approximately 100% when administered in the fed state.

1.2.1.6 General Toxicology

Oral VT-1161 was evaluated in general Good Laboratory Practice toxicity studies of up to 6 months and 9 months in duration in rats and dogs, respectively. Rats were more sensitive to the toxicological effects of oral administration of VT-1161 than dogs. The no observable adverse effect level (NOAEL) for the 6-month rat toxicity study was determined to be 0.5 mg/kg/day, based on an increase in incidence and severity of chronic progressive nephropathy, a rat-specific finding. The NOAEL for liver findings was 1.5 mg/kg, based on adverse findings at the high dose of 5 mg/kg/day including a minimal increase in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and an increase in frequency of minimal focal necrosis and single cell necrosis. Findings of liver hypertrophy, sub-capsular necrosis and multinucleated hepatocytes were considered rat-specific and associated with metabolic adaptation. Focal necrosis may be an exaggerated response to hepatocellular hypertrophy which is known to cause sub-capsular and single cell necrosis. The findings were reversible and similar to the findings observed in a prior 28-day study in the rat, providing support that the increased treatment duration in the 6-month rat study did not result in new findings of clinical concern. At the 1.5 mg/kg dose at steady state on Day 182, maximum plasma concentration (C_{max}) was 4,055 ng/mL and area under the curve (AUC_{0-24}) was 81,900 ng·h/mL. The NOAEL for the 9-month dog study was determined to be the high dose of 17 mg/kg/day (Day 273 C_{max} was 74,700 ng/mL and AUC_{0-24} was 1,675,000 ng·h/mL), as no adverse findings were identified. The NOAEL in the previous 28-day dog study was 10 mg/kg/day, based on decreased body weight and mild effects on lymphoid organs including increased tingible body macrophages in the mandibular and mesenteric lymph nodes and in the Peyer's patches at 30 mg/kg and higher. These findings were largely reversed during the recovery period.

1.2.1.7 Genotoxicity

VT-1161 was found to be negative for genotoxicity in the Ames bacterial reverse mutation assay, the chromosome aberration assay in human peripheral lymphocytes and the *in vivo* bone marrow micronucleus assay in rats.

1.2.1.8 Reproductive Toxicology

VT-1161 at doses resulting in maternal toxicity (clinical signs and decrease in body weights) did not cause alterations in uterine and ovarian parameters in embryofetal development studies in rats and rabbits. Mean fetal body weights were slightly reduced in rabbits in the high dose group as a direct result of maternal toxicity and decreased maternal body weights. No external, visceral and skeletal malformations and variations were observed at any of the dose levels evaluated. There were no effects on male or female fertility at clinically relevant doses.

1.2.1.9 Safety Pharmacology

The effects of VT-1161 on the neurological and pulmonary systems were evaluated in Sprague-Dawley rats. The data demonstrated that there were no VT-1161-related effects in either the neuropharmacological or pulmonary studies in rats given an oral dose of up to 1,000 mg/kg VT-1161, the highest dose tested.

Evaluation of cardiovascular function in telemetered dogs revealed no treatment-related changes in heart rate, blood pressure, cardiac rhythm or morphology, including the QT/QTc (Fridericia correction) interval, at oral doses up to 300 mg/kg, the highest dose tested.

1.2.1.10 In *Vitro* Cytochrome P450 Interactions

VT-1161 inhibited cytochrome P450 enzymes with the following potencies: CYP1A2 (half maximal inhibitory concentration [IC_{50}] ≥10 μM), CYP2B6 (IC_{50} = 4.0 μM), CYP2C8 (IC_{50} = 1.4 μM), CYP2C9 (IC_{50} ≥10 μM), CYP2C19 (IC_{50} = 9.7 μM), CYP2D6 (IC_{50} = 9.4 μM), and CYP3A4 (IC_{50} = 9.6 μM [testosterone], IC_{50} ≥10 μM [midazolam]). Based on the high plasma protein binding of VT-1161, no clinically significant drug-drug interactions are expected.

1.2.1.11 Effects of VT-1161 on Cardiac Repolarization

An *in vitro* human ether-à-go-go related gene study was conducted to assess the potential of VT-1161 to inhibit the repolarizing current of the cardiac action potential. VT-1161 inhibited the human ether-à-go-go related gene potassium current by 94.7 ± 1.3% at 6 μM. The IC_{50} was calculated to be 1.9 μM (Hill coefficient = 2). However, a cardiovascular safety study in dogs showed that VT-1161 was well tolerated and did not induce any deleterious cardiovascular effects or affect QT intervals at test doses of up to 300 mg/kg, the highest dose tested, with exposures reaching 24,000 ± 6,881 ng/mL at 30 hours post-dose.

1.2.2 Clinical Studies

1.2.2.1 Phase 1 Studies

VT-1161 has been evaluated in 4 Phase 1 trials, a single ascending dose trial, a multiple ascending dose trial, a DDI study with midazolam as a sensitive substrate, and an ethnic PK study comparing Japanese and Western subjects. The primary objectives of these studies were to evaluate the safety and tolerability, PK and drug interaction potential of VT-1161 in healthy adult subjects. Detailed descriptions of the trials can be found in the VT-1161 Investigational Brochure.

1.2.2.1.1 Single Dose-Escalation Study (Study VMT-VT-1161-CL-001)

Study VMT-VT-1161-CL-001 was a single-center, Phase 1, double-blind, randomized, placebo-controlled, dose-escalating study in healthy adult subjects. The study was designed to evaluate the safety, tolerability, and PK of single oral doses of VT-1161. Sixty-four subjects (43 males and 21 females) between 18 and 55 years of age were enrolled in 8 dose groups. Within each dose-group, 6 subjects received VT-1161 and 2 subjects received placebo. In the first 7 cohorts, escalating single oral doses (5, 10, 20, 40, 80, 160, and 320 mg) or matching placebo were administered in the fasted state. An 8th cohort received a single 320 mg oral dose of VT-1161 or matching placebo after ingesting a high-fat breakfast. Subjects in Cohorts 1 to 6 were followed for 14 days for safety and PK assessments. Visits on Days 28 and 42 were added for Cohorts 7 and 8. Dose escalation proceeded only after safety and PK of the previous dose was determined.

There were no deaths or serious adverse events (SAEs) reported. There were no treatment-emergent adverse events (TEAEs) that led to discontinuation from the study.

Overall, mean changes from baseline in safety parameters (hematology, chemistry, urinalysis, vital signs, and electrocardiogram [ECG]s) were generally small and were considered not clinically significant. None of the treatment-emergent physical examination abnormalities were of clinical significance. The maximum tolerated dose for the study was the highest dose administered, 320 mg, administered in the fed state.

Following oral administration of VT-1161 in the fasted state, median time to reach maximum plasma concentration (T_{max}) ranged from 4 to 10 hours. Overall, C_{max} increased slightly less than proportional to dose. The area under the plasma concentration versus time curve from time zero to infinity (AUC_{inf}) values generally increased with increase in dose, ranging from an average of 16,145 ng•hr/mL at 20 mg to 241,971 ng•hr/mL at 320 mg. The mean half-life ranged from 393 to 1,467 hours. Administration of 320 mg VT-1161 with a standard high-fat meal resulted in higher plasma concentrations than those observed following 320 mg in the fasted state in a separate group

of subjects. Average fasting C_{max} was 338 ng/mL and this increased to 988 ng/mL in the fed state. AUC_{inf} also increased from 241,971 ng•hr/mL when subjects were fasted to 953,119 ng•hr/mL with a high-fat meal.

1.2.2.1.2 Multiple Dose-Escalation Study (Study VMT-VT-1161-CL-002)

Study VMT-VT-1161-CL-002 was a Phase 1, single-center, randomized, double blind, placebo-controlled, multiple dose-escalating study in healthy adult subjects. The study was designed to evaluate the safety, tolerability, and PK of multiple oral doses of VT-1161. In addition to plasma PK, concentrations of VT-1161 in nails and skin were assessed. A total of 32 subjects participated in the study and received VT-1161 at 40, 80, 160 or 320 mg or placebo once daily for 7 days after ingestion of a high-fat meal. In each cohort of 8 subjects, 6 subjects received VT-1161, and 2 subjects received placebo. Subjects were followed for safety and PK assessments for 42 days after the last dose of study drug.

There were no deaths or SAEs reported. Most TEAEs were mild in intensity and no severe TEAEs were reported.

Mean changes from baseline in safety parameters (hematology, chemistry, coagulation, urinalysis, vital signs, and ECGs) were generally small and not considered clinically significant. There was no evidence of any clinically significant effect of VT-1161 on physical examinations in any dose group at any time point. The maximum tolerated dose for the study was the highest dose administered, 320 mg, administered once daily for 7 days in the fed state.

Following oral administration of VT-1161 in the fed state, median T_{max} values ranged from 4 to 6 hours after dosing. The increase in mean C_{max} was nearly proportional to dose over the 40 to 320 mg dose range. The concentrations were 3 to 4-fold higher on Day 7 than they were on Day 1, indicating accumulation during the 7-day dosing interval, with a mean C_{max} of 3,300 ng/mL on Day 7 at 320 mg. The area under the plasma concentration versus time curve over the dosing interval (AUC_{τ}) values on Day 7 also increased nearly proportionally to dose over the 40 to 320 mg dose range. The mean half-life ranged from 1,905 to 3,046 hours.

1.2.2.1.3 Drug-Drug Interaction Study (Study VMT-VT-1161-CL-007)

Study VMT-VT-1161-CL-007 was a Phase 1, single-center, open-label study in healthy adult subjects to evaluate the effect of single and multiple oral doses of VT-1161 when co-administered with single oral doses of midazolam (DDI cohort) and to evaluate the PK of a single oral dose of an alternate strength of VT-1161 alone (pharmacokinetic evaluation [PKE] cohort). All dosing

was conducted 30 minutes after the start of a high-fat, high-calorie meal. A total of 36 subjects were enrolled in the study.

In the DDI cohort, 28 subjects were enrolled in a fixed-sequence design to receive a 2-mg oral dose of midazolam on Day 1, followed by 14 daily 600 mg oral doses of VT-1161 (4 x 150 mg tablets) on Day 3 through Day 16 with single 2 mg oral doses of midazolam on Day 3 and Day 16. Subjects were followed for safety, tolerability and PK assessments through Day 17, 1 day after the last dose of study drug. Twenty-four subjects in the DDI cohort completed the study and 4 subjects withdrew from the study prior to completion; 2 subjects voluntarily withdrew consent and 2 subjects withdrew due to an AE (discussed in more detail below).

There were no deaths reported in the study. One SAE (acute psychosis) was reported in a subject in the DDI cohort on Day 11 of the study, leading to discontinuation. The Investigator determined the subject likely had a pre-existing psychiatric condition based on patient report and assessed causality as unlikely-related to VT-1161. One additional subject in the DDI cohort withdrew from the study due to an AE of abnormal ECG on Day 3 of the study. The AE occurred prior to the first dose of VT-1161; the Investigator assessed causality as unrelated to study drug. Otherwise, mean changes from baseline in safety parameters (hematology, chemistry, coagulation, urinalysis, vital signs, and ECGs) in both the DDI and PKE cohorts were generally small and not considered clinically significant and there was no evidence of any clinically significant effect of VT-1161 on physical examinations in either cohort.

In the DDI cohort, midazolam mean plasma C_{max} increased 30% and AUC_{inf} decreased 15% on Day 3 (after the first dose of VT-1161) relative to Day 1 (midazolam alone). Midazolam mean plasma C_{max} decreased 3% and AUC_{inf} decreased 37% on Day 16 (after 14 daily doses of VT-1161) relative to Day 1 (midazolam alone).

In the PKE cohort, 8 subjects were enrolled to receive a single 600 mg oral dose of VT-1161 (2 x 300 mg tablets) on Day 1. Subjects in the PKE cohort were followed for safety, tolerability and PK assessments through Day 2, 1 day after the dose of study drug. All 8 subjects in the PKE cohort completed the study. VT-1161 mean plasma C_{max} and AUC_{0-24} values after a single oral administration of 600 mg VT-1161 (2 x 300 mg) on Day 1 were 1,946 ng/mL and 28,070 ng•hr/mL, respectively. These values are similar to VT-1161 mean plasma C_{max} and AUC_{0-24} values after a single oral administration of 600 mg VT-1161 (4 x 150 mg) in the DDI cohort (1,994 ng/mL and 25,330 ng•hr/mL, respectively), indicating the bioavailability of the 2 strengths of tablets is similar.

1.2.2.1.4 Japanese Bridging Study (Study VMT-VT-1161-CL-008)

Study VMT-VT-1161-CL-008 was a single-center, open-label study in healthy adult Japanese and Western subjects. The objective of this ethno-bridging study was to evaluate the safety, tolerability, and PK of VT-1161 in these 2 ethnic populations after subjects received 14 once daily oral doses of VT-1161 administered in the fed state. There was a total of 51 subjects enrolled. In the 300-mg dosage-group, there were 13 Japanese and 14 Western subjects. In the 600 mg dosage group, there were 12 Japanese and 12 Western subjects. The mean age of subjects was 36.5 years, ranging from 19 to 55 years across treatment groups. The subjects were evenly divided by sex across all groups and the race of the Western subjects was evenly divided by white and black.

The study drug was overall well tolerated by both Western and Japanese subjects. There were no significant differences between the 2 populations in any of the safety assessments. A slight increase in AEs was seen in the 600 mg dosage group as compared with the 300 mg dosage group, but no SAEs were observed. Only 1 subject was withdrawn from the study for an AE of rash (subject request), which was categorized as an unlikely-related TEAE. There was 1 pregnancy in a subject who was non-compliant with contraception requirements, which was electively terminated by the subject.

Of the 51 subjects enrolled in the study, 11 Japanese subjects from both dose groups and 12 Western subjects from both dose groups were included in the full PK analysis population. Trough concentrations on Days 1 through 14 rose each day; thus, steady-state conditions had not been met by Day 14. Larger differences between the 2 ethnic groups were seen in C_{max} and AUC_{0-72} following the 300 mg dose compared with the 600 mg dose. At the 300 mg dose, C_{max} and AUC_{0-72} were approximately 40% higher in Japanese subjects compared with Western subjects. At the 600-mg dose, C_{max} and AUC_{0-72} were approximately 10% higher in Japanese subjects compared with Western subjects. However, median T_{max} was similar across doses at 4 hours for Japanese subjects at both the 300 mg and 600 mg dosages and 6 hours for Western subjects at both the 300 mg and 600 mg dosages. The terminal elimination phase was very flat and half-life exceeded 1800 hours. Total clearance following the 300-mg dose was 1.642 L/hr for the Japanese subjects compared with 2.332 L/hr for the Western subjects. Following the 600 mg dose, clearance was similar for the Japanese and Western subjects (2.000 and 2.086 L/hr, respectively).

1.2.2.2 Phase 2 Studies

1.2.2.2.1 Dose Ranging Study in Tinea Pedis (Study VMT-VT-1161-CL-003)

VMT-VT-1161-CL-003 was a Phase 2a, randomized, double-blind, dose-ranging study to evaluate the efficacy and safety of VT-1161 over-encapsulated tablets compared to placebo in the treatment of subjects with moderate to severe interdigital tinea pedis. A total of 50 subjects participated in the study across 4 dose groups: 1) VT-1161 200 mg once daily for 4 days, followed by 50 mg once daily for 10 days (low dose); 2) VT-1161 600 mg once daily for 4 days, followed by 150 mg once daily for 10 days (mid-dose); 3) 600 mg twice daily for 4 days, followed by 300 mg once daily for 10 days (high dose; or 4) placebo matching the VT-1161 treatment regimen. VT-1161 plasma concentrations increased with dose and were as high as 6,230 ng/mL on Day 14 in the 600 mg twice daily/300 mg once daily dose group. Subjects were enrolled into the high-dose cohort following an interim analysis that included safety data generated through the test of cure (TOC) visit (Day 42) of the 2 lower dose groups.

VT-1161 was safe and well tolerated at all dose levels through 6 months of follow-up. No SAEs were reported. Most AEs reported were mild to moderate in severity and considered unrelated to study drug. A single VT-1161 treatment related AE was reported (rash) that was considered by the Investigator to be "possibly related." The subject discontinued treatment after the first dose, and the rash completely resolved by the following day. There were no clinically significant treatment-emergent changes in vital signs, physical findings, ECGs, or laboratory parameters. One subject experienced a significant elevation of creatine kinase (CK) along with a slight increase in ALT and AST that was associated with a rigorous exercise program. These changes were considered unrelated to treatment and all enzyme levels returned to normal at a subsequent follow-up visit.

At the Day 42 TOC visit, 42%, 42%, 50% and 0% of subjects receiving low dose, mid-dose or high dose VT-1161 or placebo were determined to have achieved effective therapeutic cure (defined as having a total severity score of ≤2 with no individual severity score of >1, and also, having negative mycology [culture and KOH]) in the intent-to-treat (ITT) population.

1.2.2.2.2 Dose Ranging Study in Acute Vulvovaginal Candidiasis (Study VMT-VT-1161-CL-004)

VMT-VT-1161-CL-004 was a randomized Phase 2a, double-blind, dose ranging study to evaluate the efficacy and safety of VT-1161 over-encapsulated tablets compared to fluconazole in the treatment of 55 subjects with moderate to severe acute VVC. A total of 55 subjects with moderate-to-severe acute VVC (severity score ≥6 and a positive fungal KOH test) participated in the study

across 4 dose groups: 1) VT 1161 300 mg once daily for 3 days, 2) 600 mg once daily for 3 days, 3) 600 mg twice daily for 3 days, or 4) a single dose of fluconazole 150 mg followed by matching placebo. Subjects were enrolled into the high-dose cohort following an interim analysis that included safety data generated through the TOC visit (Day 28) of the 2 lower dose groups. An additional interim analysis was conducted when the high-dose subjects had completed their TOC visit.

VT-1161 was determined to be safe and well tolerated at all dose levels through Day 28. No SAEs were reported and no subjects discontinued because of an AE. Most AEs reported were considered unrelated to study drug and were mild in severity. There were few treatment-related TEAEs of clinical concern. Most TEAEs were reported in the low- and mid-dose cohorts and only 1 TEAE (insomnia) was noted in the high-dose cohort. One subject developed urticaria that was considered possibly related to study drug and which resolved with prednisone. There were no clinically significant treatment-emergent changes in vital signs, physical findings, ECGs or laboratory parameters.

The efficacy of VT-1161 in the treatment of moderate-to-severe acute VVC was evaluated at the TOC visit in the ITT population (defined as all randomized subjects receiving at least 1 dose of study drug) and the per protocol (PP) population (defined as subjects that were compliant with all key aspects of the protocol). Subjects in the ITT population were randomized into the VT-1161 300 mg once daily for 3 days (n = 14), VT-1161 600 mg once daily for 3 days (n = 12), VT-1161 600 mg twice daily for 3 days (n = 14) or fluconazole (n = 15). Effective clinical cure rate (defined as having a total severity score of 0 or 1 and a negative culture) were 29%, 83%, 86% and 73%, respectively. Subjects in the PP population achieved effective therapeutic cure at a rate of approximately 87%, 86%, 86% and 75%, respectively, in the low-dose, mid-dose, or high-dose VT-1161 or fluconazole groups at the Day 28 TOC visit.

1.2.2.2.3 Phase 2b Study in Subjects with Distal and Lateral Subungual Onychomycosis of the Toenail (VMT-VT-1161-CL-005)

In this Phase 2b study, the safety, tolerability, PK and efficacy of VT-1161 in subjects with distal and lateral subungual onychomycosis of the toenail were evaluated. A total of 259 subjects participated in the study in 5 treatment groups and were administered either:

- Low dose 12-week: Loading doses of 300 mg once daily for 2 weeks, then 300 mg once weekly for 10 weeks, followed by placebo for 12 weeks.

- Low dose 24-week: Loading doses of 300 mg once daily for 2 weeks, then 300 mg once weekly for 22 weeks.
- High dose 12-week: Loading doses of 600 mg once daily for 2 weeks, then 600 mg once weekly for 10 weeks, followed by placebo for 12 weeks.
- High dose 24-week: Loading doses of 600 mg once daily for 2 weeks, then 600 mg once weekly for 22 weeks.
- Matching placebo

Subjects in all cohorts were followed for 60 weeks. Consenting subjects were enrolled into an extension study to assess the long-term safety and PK of VT-1161 through Week 96.

The incidence of adverse events (AEs) was balanced across the VT-1161 treatment arms and placebo. A total of 148 subjects (57%) had at least 1 TEAE, and the frequency was within the range of 49% to 67% for all treatment groups. The majority of TEAEs were considered by the Investigator to be mild or moderate and unrelated to study drug. Most TEAEs were transient and occurred during the first 12 weeks of treatment for all treatment groups, including placebo. Nineteen subjects reported related TEAEs through Week 60. Sixteen subjects were on VT-1161 and three subjects were on placebo. The only related TEAE reported by more than 2 subjects was nausea. Eleven subjects reported a total of 16 SAEs, which were considered unrelated to study drug.

The incidence of study drug related TEAEs was within the range of 6% to 11% for all treatment groups, with the highest frequency in the 600 mg 24-week group. The most common (≥2 total subjects) TEAEs that were considered related to VT-1161 were nausea, dysgeusia, dizziness, constipation, and decreased appetite. The most common TEAE that was considered related to placebo was dizziness.

The incidence of TEAEs leading to study drug discontinuation was low, in the range of 0% to 6% for all treatment groups.

There were no clinically-relevant findings noted by the Investigators with vital signs, physical exam findings or ECGs.

There was no obvious clinically-relevant effect of VT-1161 on chemistry, hematology or urinalysis parameters.

Overall, VT-1161 was safe and well-tolerated at all doses and treatment durations including the highest dose and longest duration evaluated of 600 mg 24-week treatment group. The TEAEs were typical of the subject population being studied and were generally balanced across the VT-1161 treatment and placebo group.

The primary efficacy endpoint was complete cure at Week 48. The proportion of subjects in the ITT population with complete cure at Week 48 ranged from 32% to 42% in the VT-1161 treatment groups, with the lowest rate in the 300 mg 12–week treatment group and the highest rate in the 600 mg 12–week treatment group. No subjects receiving placebo experienced complete cure at Week 48. The proportion of ITT subjects with complete cure was statistically significantly higher for all VT-1161 treatment groups compared with placebo at Week 48 ($p<0.001$).

Overall, the efficacy at Week 48 was clearly demonstrated in all the VT-1161 treatment groups, with little to no improvement seen in the placebo group.

1.2.2.2.4 Phase 2b Study in Subjects with Recurrent Vulvovaginal Candidiasis

In this Phase 2b study, the safety, tolerability, PK and efficacy of VT-1161 in subjects with recurrent vulvovaginal candidiasis was evaluated. A total of 215 subjects participated in the study, were randomized to 5 treatment groups and were administered either:

- Low dose 12-week: Loading doses of 150 mg once daily for 7 days, then 150 mg once weekly for 11 weeks, followed by placebo for 12 weeks.
- Low dose 24-week: Loading doses of 150 mg once daily for 7 days, then 150 mg once weekly for 23 weeks.
- High dose 12-week: Loading doses of 300 mg once daily for 7 days, then 300 mg once weekly for 11 weeks, followed by placebo for 12 weeks.
- High dose 24-week: Loading doses of 300 mg once daily for 7 days, then 300 mg once weekly for 23 weeks.
- Matching placebo

In general, the incidence of AEs was balanced across the VT-1161 treatment arms and placebo. Two subjects discontinued VT-1161 because of a TEAE. Of these two, only one TEAE was considered related to VT-1161 by the study investigator. Most TEAEs were considered unrelated to study drug and were mild or moderate in severity. Six SAEs were reported through Week 48

of the study, none of which were considered related to study drug by the investigator. Interestingly, a higher incidence of bacterial vaginosis and urinary tract infections was reported in the placebo arm.

There were no clinically-relevant findings noted by the investigators regarding vital signs, physical exam findings or ECGs. There was no obvious clinically-relevant effect of VT-1161 on chemistry, hematology or urinalysis parameters.

The primary efficacy outcome measure 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. Culture-verified acute VVC was defined as a positive fungal culture for *Candida* species associated with a clinical signs and symptoms score of ≥ 3. The proportion of subjects with one or more culture-verified acute VVC episode through Week 48 was lower in VT-1161 dosing regimens: 4.8% in 150 mg 12 weeks, 7.0% in 150 mg 24 weeks, 0.0% in 300 mg 12 weeks, and 4.9% in 300 mg 24 weeks, treatment groups compared with 52.2% in the placebo group. The difference was statistically significant in the VT-1161 dosing regimens compared with placebo ($p<0.0001$).

In conclusion, VT-1161 was determined to be efficacious, safe and well tolerated at all dose levels through the final visit at Week 48 of the study.

1.3 Study Rationale

RVVC can be treated with topical and/or oral agents and patients may receive maintenance treatment for up to 6 months or longer once the acute infection has resolved. For most patients, available agents do not provide the desired delay to recurrence of an acute VVC episode, underlining the need for more effective treatments for RVVC. Fluconazole has been used to treat acute VVC episodes in patients with recurrent disease. However, fluconazole has relatively lesser activity against some non-*albicans* species that are more common in patients with complicated VVC. The current study has been designed to compare the ability of a short dosing regimen of VT-1161 or fluconazole in their ability to effectively treat the acute VVC infection in women with RVVC.

VT-1161 has demonstrated superior in vitro antifungal activity when compared to fluconazole when tested against clinical isolates collected in the recently completed Phase 2b RVVC study VMT-VT-1161-CL-006. The MIC ranges for VT-1161 and fluconazole against the *C. albicans* isolates collected during the study (n = 355) were between <0.0005 – 0.125 μg/mL and <0.06 – 4 μg/mL, respectively. When all 413 collected *Candida* spp. isolates were considered, the

MIC ranges for VT-1161 and fluconazole were <0.0005 – >0.5 µg/mL and <0.06 – 32 µg/mL, respectively. The mean MIC_{50} values for VT-1161 and fluconazole were 0.004 µg/mL and 0.125 µg/mL, respectively, and the MIC_{90} values for VT-1161 and fluconazole were 0.06 µg/mL and 4 µg/mL, respectively (Table 4).

Table 4. MIC Values of VT-1161 and Fluconazole in µg/mL for 413 *Candida* spp. Isolates Derived From Phase 2b RVVC Study

MIC Values	VT-1161	Fluconazole
Range	<0.0005 – >0.5	<0.06 – 32
MIC_{50}	0.004	0.125
MIC_{90}	0.06	4

Source: Report VMT-CWRU-VT-1161-CL-006; Determination of the Minimum Inhibitory Concentration of VT-1161 Against *Candida* Strains Obtained from Clinical Trial VMT-VT-1161-CL-006.
Abbreviations: MIC, minimum inhibitory concentration.

These data suggest that VT-1161 has the ability to treat the acute infection in the RVVC patient population and warrant further clinical investigation evaluating its effectiveness compared to current standard-of-care.

While approved oral antifungal agents often offer improved efficacy, they suffer from safety issues associated with their narrow therapeutic windows and off target toxicity. Since VT-1161 is much more selective for fungal CYP51 and CYP metabolizing enzymes than currently used oral agents, the probability of safety issues, including hepatotoxicity and DDIs, should be significantly reduced, as evidence in the clinical safety data generated with VT-1161 to date. The PK profile and extended half-life associated with VT-1161 should also limit recurrence of VVC.

1.3.1 Rationale for Induction Phase Treatment

Fluconazole is an approved treatment for acute VVC and is used off-label to treat patients with recurrent disease. The proposed dose regimen of 3 doses of over-encapsulated fluconazole taken 72 hours apart corresponds to a regimen that is often used as the standard of care and has been regularly employed during the induction phase of similar clinical studies designed to study RVVC.

1.3.2 Dosing Regimen for VT-1161 and Fluconazole with Matching Placebo

At Screening, subjects will be randomly assigned to receive one of the following treatment groups:

- VT-1161: Loading dose of 600 mg on Day 1 and 450 mg on Day 2, then 150 mg once weekly for 11 weeks.

- Fluconazole: Three doses of 150 mg every 72 hours, then placebo once weekly for 11 weeks.

The rationale for dose selection is provided in Section 4.4, Design Justification.

1.4 Potential Risks and Benefits of Participating in the Study

The Phase 1, Phase 2a, and Phase 2b studies with VT-1161 incorporated monitoring for AEs often reported with other azole antifungal drugs. No clinically significant study drug related AEs were observed in clinical studies with VT-1161, suggesting that it may be better tolerated than commonly used azole agents.

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 VVC episode in RVVC subjects.

Secondary:

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

3 STUDY ENDPOINTS

The primary efficacy outcome measure is the proportion of subjects with one or more culture-verified acute VVC episodes (post-randomization through Week 50) in the ITT population, which will include the subjects who failed clearing their infection during the Induction Phase. 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.

Secondary:

- 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 of ≥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* during the Maintenance Phase.

4 STUDY DESIGN

4.1 Overall Study Design

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. The study is designed 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 RVVC.

Subjects must have a history of RVVC, defined as at least 3 episodes of acute VVC in the past 12 months, as described below:

- Subjects must have an acute VVC episode at the time of Screening, with a documented positive KOH performed at the investigative site
- Subjects must also have had 2 or more additional episodes of acute VVC in the past 12 months, with at least 1 of the episodes documented by a positive confirmatory laboratory test (i.e., culture, PCR, Affirm test, KOH test, a documented Pap test, or other approved diagnostic test)

The study consists of two Phases: 1) an Induction Phase for the treatment of the acute VVC infection in which subjects will be randomly assigned to receive 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 and matching placebo capsules or 3 sequential 150 mg oral doses (every 72 hours) of over-encapsulated fluconazole together with matching placebo capsules, and 2) a Maintenance Phase in which subjects will receive VT-1161 or placebo for 11 weeks and will then enter a 37-week follow-up period.

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, weight and height, ECG and laboratory tests, reviewing clinical signs and symptoms of vulvovaginitis, performing a complete physical examination including speculum examination of the vagina, performing a 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 will have a composite vulvovaginal signs and symptom score of ≥3 as outlined in Section 9.1.7, a positive local KOH that confirmed the presence of yeast, and must meet other initial entry criteria.

Once eligibility is confirmed, subjects will be randomized and enter the Induction Phase. During the Induction Phase, the presenting acute VVC infection 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 for evaluation and, if the acute VVC infection has resolved (defined by a signs and symptoms score of <3), they will enter into the Maintenance Phase to receive either VT-1161 or a matching placebo regimen. 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. If the acute VVC has not resolved (defined by a signs and symptoms score of ≥3), the subject will be considered an Induction failure and encouraged to see their physician for further evaluation and follow-up care.

4.2 Treatment Arms and Duration of Study

Subjects will be randomized in a 2:1 ratio to receive VT-1161 or fluconazole and placebo.

The duration of individual subject participation will be approximately 50 weeks: including the 2-week Induction Phase, the 11-week Maintenance Phase, and 37 weeks of follow-up. Assessments and procedures will be performed as outlined in Table 1. Schedule of Assessments and Procedures. Subjects who return to the clinic for a recurrent VVC episode should be evaluated as per the unscheduled visit noted in the Schedule of Assessment and Procedures.

The planned study duration is approximately 18 months from Screening of the first subject until the last follow-up of the last subject.

4.3 Number of Subjects

Approximately 360 screened and 180 randomized subjects are planned for this study. Assuming a 20% discontinuation rate for the remainder of the study, approximately 144 subjects are expected to complete the study.

Subjects will be enrolled at approximately 45 U.S. sites.

4.4 Design Justification

One of the study goals will be to compare the efficacy of oral VT-1161 versus fluconazole in the treatment of acute VVC episodes in RVVC subjects. The proposed dosing regimen will incorporate an Induction Phase to treat the initial acute infection with either fluconazole or VT-1161.

The fluconazole dosing regimen to be employed in the Induction Phase is in alignment with the recommendation proposed by the Infectious Disease Society of America (IDSA) for the treatment of vulvovaginal candidiasis, in which fluconazole, 150 mg, is given every 72 hours for a total of 3 doses. This is recommendation is strongly supported by IDSA and for which high-quality evidence is available to support its clinical effectiveness.

VT-1161 has previously been evaluated in a Phase 2a multi-center, randomized, double-blind, active-controlled, parallel-group, dose-ranging study in patients with moderate-to-severe acute VVC (described in Section 1.2.2.2.2). A total of 55 subjects with moderate-to-severe acute VVC (severity score ≥6 and a positive fungal KOH test) participated in the study across 4 dose groups: 1) VT-1161 300 mg qd for 3 days; 2) 600 mg qd for 3 days; 3) 600 mg bid for 3 days; or 4) a single dose of fluconazole 150 mg followed by matching placebo. VT-1161 was shown to safe and well tolerated when administered for 3 days. There were no serious AEs reported and no TEAEs led to study discontinuation. No safety signals of clinical concern were observed from the safety assessments.

The efficacy of VT-1161 in the treatment of moderate-to-severe acute VVC was evaluated at the TOC visit in the Per Protocol population at the Day 28 test of cure TOC visit was, 87%, 86%, 86%, and 75% of subjects receiving the low , mid-, or high-dose VT-1161 or comparator arm of fluconazole, respectively, achieved an effective therapeutic cure (defined as having a total clinical signs and symptoms severity score of ≤1 and a negative culture for *Candida* species) in the Per Protocol population

It is predicted based on plasma levels obtained in previous clinical studies that the proposed loading dose regimen of 600 mg on Day 1 and 450 mg on Day 2 will provide for clinically effective plasma levels (approximately 2 µg/mL) to treat the presenting acute *Candida* spp. infection a manner that will afford comparison of the efficacy of oral VT-1161 and fluconazole in the treatment of an acute VVC episode in subjects with RVVC.

Similar and higher doses of VT-1161 have been studied previously in subjects with onychomycosis (VMT-VT-1161-CL-005), with a maximum high dose of 600 mg once daily for 2 weeks, then 600 mg once weekly for 22 weeks administered (see Section 1.2.2.2.3).

The proposed VT-1161 dosing regimen for the current Phase 3 studies will also incorporate a 150 mg once weekly maintenance dose phase for 11 weeks. Based on the PK results from the Phase 2b study, it is expected that this will provide a mean plasma concentration of approximately 2.5 µg/mL at the end of the dosing period (Week 14).

4.4.1 Justification for Inclusion of Adolescents in the Study

Vulvovaginal candidiasis, and especially RVVC, is rare in pre-menarchal girls (typically pre-adolescents less than 12 years of age) and epidemiological data is generally lacking for this population.

Adolescent females (ages 12 to 17 years, inclusive) represent a menarchal population that is newly influenced by reproductive hormones. The changes in reproductive hormones in adolescents cause vast changes in tissues and may increase the susceptibility to VVC. In this population, cases of VVC and RVVC exist but are substantially less common than in adult females. While 75% of healthy women will likely experience one episode of VVC in their lifetime, and potentially 9% will be characterized as having recurrent disease, the prevalence of symptomatic acute VVC in adolescents is less than 2% of the population and there is no published data that addresses the incidence of RVVC in this patient population (Fidel, 2002; Blostein, 2017; Barousse, 2004). Presenting symptoms of VVC in menarchal adolescents are similar to those in the adult population, and treatment typically consists of topical antifungal preparations while oral antifungal agents are prescribed only in severe or complicated cases (Joishy, 2005). The dose and administration of the agents used in adolescents are the same as those used in adult females with VVC and RVVC.

The United States FDA Draft Guidance Vulvovaginal Candidiasis: Developing Drugs for Treatment states that while uncomplicated VVC is unlikely to occur in healthy pre-menarchal girls, post-menarchal adolescent girls with VVC should be included in Phase 3 trials. Accordingly, the present study will follow guidance received by the United States FDA reviewers and will allow enrollment of subjects 12 to 17 years of age (inclusive) to collect as much information as possible on the treatment of the adolescent population with RVVC.

5 SELECTION OF STUDY POPULATION

The following criteria for enrollment must be followed explicitly. A subject will not be enrolled unless the following inclusion/exclusion criteria are met. The Investigator or other study site personnel must record in the source documents (e.g., the site's chart) and case report form (CRF) that the informed consent document or assent (for those ages 12-17) was signed and dated prior to any study procedures. The presence of inclusion criteria and absence of exclusion criteria will be verified by the Investigator in the subject's clinic chart.

5.1 Inclusion Criteria

1. Subjects must be generally healthy, non-pregnant, post-menarchal females 12 years of age and older as of Screening.
2. Subjects must have a history of recurrent VVC as defined by three (3) or more patient reported and/or laboratory confirmed episodes of acute VVC in the past 12 months including the episode confirmed at Screening, with at least one episode (not including the current episode) documented by a positive culture, PCR, Affirm test, KOH test, or a documented Pap test in the prior 12 months revealing filamentous hyphae/pseudohyphae and/or budding yeast cells.
3. Subjects must have an acute VVC infection at Screening, defined as a total signs and symptoms score of ≥3 and a positive KOH wet mount preparation from a vaginal smear revealing filamentous hyphae/pseudohyphae and/or budding yeast cells.
4. Subjects must have a composite vulvovaginal signs and symptoms score of <3 at the Day 14 Visit.
5. Subjects must have a documented Pap test results at Screening or within the current standard of care guidelines for the appropriate age requirement, reported as either "negative for intraepithelial lesion or malignancy" or "ASCUS-atypical squamous cells of undetermined significance" (not applicable to subjects with a history of total hysterectomy).
6. Subjects must be suitable candidates for oral therapy and be able to swallow capsules intact.
7. Subjects must be willing and able to provide written informed consent or assent (for those ages 12-17) and authorization for use of protected health information.
8. Subjects must be willing and able to comply with protocol requirements, instructions, and protocol-stated restrictions and be likely to complete the study as planned.
9. Subjects of non-childbearing potential must meet the requirements defined below:

a. Pre-menopausal with documentation of surgical sterilization (i.e., hysterectomy, bilateral tubal ligation, bilateral oophorectomy, or bilateral salpingectomy) at least 3 months prior to study entry.

b. Post-menopausal defined as amenorrhea for at least 12 months following cessation of all exogenous hormonal treatments at Screening.

10. Subjects of childbearing potential (includes ages 12 to 17) must use 1 of the following methods of contraception during the study through Week 50:

OPTION 1 - Highly effective methods that can be used alone:

1. Copper intrauterine device used continuously and successfully for at least 90 days prior to first dose of study drug[a]
2. Levonorgestrel-releasing intrauterine system used successfully for at least 90 days prior to first dose of study drug[a]
3. Progestin implant used successfully for at least 90 days prior to first dose of study drug[a]
4. Monogamous with a vasectomized male partner (vasectomy performed at least 6 months prior to first dose of study drug)[a]
5. Abstinence[b]

OPTION 2 – Acceptable first and second barrier methods to be used in combination:

FIRST *(Hormonal Contraception)*[a]

1. Estrogen & progestin oral contraceptives, transdermal patch or vaginal ring used successfully for at least 90 days prior to first dose of study drug
2. Progestin only oral contraceptives or injection used successfully for at least 90 days prior to first dose of study drug

SECOND *(Barrier Method)*

1. Diaphragm (with spermicide)
2. Cervical cap (with spermicide)
3. Male condom (with or without spermicide)

In addition to OPTIONS 1 and 2, subjects of childbearing potential (includes ages 12-17) may also use 1 of the following methods of contraception after completing the Induction Phase on Study Day 1 through Week 50:

OPTION 3 (Day 14 – Week 50)[c] – Acceptable first and second barrier methods to be used in combination:

FIRST *(Barrier Method)*

1. Diaphragm (with spermicide)
2. Cervical cap (with spermicide)

SECOND *(Barrier Method)*

1. Male condom (with or without spermicide)

[a] Subjects who started using an intrauterine device or any of the hormonal contraceptive methods described above less than 3 months prior to the first dose of study medication must agree to use a double-barrier method (i.e., diaphragm plus spermicide or condom) through 3 months after start of the use of the IUD or hormonal contraceptive. Similarly, subjects that claim a monogamous relationship with a vasectomized male partner where the vasectomy was performed less than 6 months prior to the first dose of study medication, must agree to use a double-barrier method (i.e., diaphragm plus spermicide or condom) through 6 months after the date of the vasectomy.

[b] Sexual abstinence is defined as refraining from heterosexual intercourse during the entire study period and where this is the usual life style of the subject. Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not considered to be acceptable methods of contraception.

[c] Because of the teratogenic risk associated with repeat dosing of fluconazole, OPTION 3 contraceptive, methods cannot be used during Screening and the Induction Phase of the study [from Screening (Day 1) until Day 14 of the study].

5.2 Exclusion Criteria

1. Subjects must not have the presence of concomitant vulvovaginitis caused by other pathogens (e.g., bacterial vaginosis, *Trichomonas vaginalis*, *Chlamydia trachomatis*, or *Neisseria gonorrhoeae*) at Screening visit (Day 1) visit.

2. Subjects must not have an active HPV infection as evidenced by visible condylomas on vulvovaginal examination at Screening (Day 1) visits.

3. Subjects must not have the presence or a history of another vaginal or vulvar condition(s) that in the Investigator's opinion would confound the interpretation of clinical response.

4. Subjects must not have a history of cervical cancer.

5. Subjects must not use any systemic (e.g., oral or injectable) corticosteroid therapy during the study or within 30 days prior to Screening; nor use of topical vulvar or vaginal steroids during the study or within 7 days prior to Screening visit. However, use of topical (no vulvar or vaginal steroids), inhaled, ophthalmic, collunarium/nasal, intraarticular and intralesional steroids is permitted.

6. Subjects must not use any systemic (e.g., oral or injectable) or topical (applied to the vulva or vaginal area) antifungal, antibacterial, or antitrichomonal drugs for the treatment of bacterial vaginosis, trichomonas, or other concomitant urogenital infection during the study (unless prescribed by the Investigator) or within 7 days prior to Screening.

7. Subjects must not be using drugs with a narrow therapeutic index that are metabolized by CYP3A4 and sensitive to induction of CYP3A4 during the study (carbamazepine, cyclosporine, fentanyl, quinidine, sirolimus and tacrolimus).

8. Subjects must not use any vaginal estrogen replacement therapy, ospemifene, Vitamin E gel capsules (vaginally) or lubricants within 7 days prior to Screening.

9. Subjects must not have a condition that would require treatment during the study with concomitant topical (applied to vulva and vagina) or systemic antimicrobial therapy for any reason.

10. Subjects must not have received an immunosuppressive medication (e.g. cyclosporine, tacrolimus, methotrexate, 6 mercaptopurine, mycophenolate, etc.), or radiation therapy within 3 months prior to Screening or have a medical condition where it would be likely that the subject may need to use these therapies during the study.

11. Subjects must not have evidence of any clinically significant major organ disease or current clinically significant infection or any other conditions (with the exception of acute VVC) that may affect the clinical assessment of RVVC per Investigator judgment.

12. Subjects must not have any comorbid condition that in the opinion of the Investigator would preclude the safe participation of the subject in the study or would prevent the subject from meeting the study requirements.

13. Subjects must not have any condition that in the opinion of the Investigator could impact drug absorption (e.g. gastrectomy, Roux-en-Y gastric bypass surgery, gastric bands or staples, etc.), distribution, or elimination.

14. Subjects must not have poorly controlled diabetes mellitus (HbA1c ≥8.5% at Screening; performed only on known diabetics or subjects suspected to have diabetes by the investigative site).

15. Subjects must not have moderate or severe hepatic and/or renal disease (defined in Appendix B and Appendix C).

16. Subjects must not have a laboratory abnormality that in the opinion of the Investigator is likely to introduce additional risk to the subject or might interfere with data interpretation. The specific findings listed below are excluded at Screening (a single repeat laboratory evaluation is allowed for eligibility determination, except for HIV, HBsAg and antibodies to hepatitis C virus):

    a. Serum ALT ≥2.0x the upper limit of normal (ULN) of the reference range.

    b. Serum AST ≥2.0x the ULN of the reference range.

    c. Serum total bilirubin ≥1.5x the ULN of the reference range, unless the elevation is consistent with Gilbert's Syndrome.

    d. Electrocardiographic QTc interval >470 msec as corrected by the Fridericia formula, or any clinically significant electrocardiographic abnormality.

    e. Positive test for antibodies to human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or antibodies to hepatitis C virus.

17. Subjects of childbearing potential must not be pregnant (positive pregnancy test at Screening), lactating, or planning to become pregnant during the study period.

18. Subjects must not have planned surgery or other medical procedures that in the Investigator's opinion would impact compliance with the protocol.

19. Subjects must not have active substance abuse (e.g., drugs of any kind, including alcohol) or any other medical, psychiatric or social condition that in the Investigator's opinion would preclude compliance with the protocol.

20. Subjects must not have received VT-1161 study medication in a previous study.

21. Subjects must not have received any IMP in a clinical trial within 5 half-lives of that IMP prior to Screening (if unknown, 60 days prior to Screening).

22. Subjects must not have a known history of intolerance or hypersensitivity to azole antifungal drugs (e.g., fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole), or any excipients of the capsule formulation.

6 INVESTIGATIONAL MEDICINAL PRODUCT

All protocol-specific criteria for administration of study treatments must be met and documented prior to IMP administration. Study treatments will be administered only to eligible subjects under the supervision of the Investigator.

6.1 Description of Investigational Medicinal Product

6.1.1 VT-1161

Active IMP will be supplied by Mycovia Pharmaceuticals (or its designee) as capsules containing 150 mg of VT-1161.

6.1.2 Fluconazole

Over-encapsulated fluconazole tablets containing 150 mg of active pharmaceutical ingredient will be provided by Mycovia Pharmaceuticals (or its designee) for use in the randomized treatment assignment during the Induction Phase.

Fluconazole tablets containing 150 mg of active pharmaceutical ingredient will be provided by the Investigator or Mycovia Pharmaceuticals (or its designee) for treatment of acute VVC episodes during the Maintenance Phase (as described in Section 7.4.2). Fluconazole will be reimbursed by Mycovia Pharmaceuticals.

6.1.3 Placebo

Two placebo products will be supplied by Mycovia Pharmaceuticals (or its designee):

- capsules matching the appearance of VT-1161 capsules
- capsules matching the appearance of the over-encapsulated fluconazole tablets

6.2 Investigational Medicinal Product Labeling and Packaging

Mycovia Pharmaceuticals (or its designee) will package the VT-1161, over-encapsulated fluconazole and placebo capsules. IMP will be supplied according to applicable regulatory requirements. Information pertaining to labeling and a description of the specific packaging and storage conditions will be supplied to the Investigator or designee.

VT-1161, over-encapsulated fluconazole, and matching placebos will be provided in 2 bottles for dosing during Days 1-7 and in a single bottle for weekly dosing through Week 14 of the study.

6.3 Investigational Medicinal Product Storage Conditions

IMP will be stored in a secure location at a controlled room temperature of 15°C to 25°C (59°F to 77°F) and protected from light and moisture. The storage of IMP will be locked with limited access, available to appropriate study personnel only.

6.4 Receipt of Supplies/Handling/Storage

Only subjects enrolled in the study may receive study treatment, and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored area in accordance with the labelled storage conditions with access limited to the Investigator and authorized staff.

Further guidance and information for final disposition of unused study treatments are provided in the Study Procedures Manual.

6.5 Investigational Medicinal Product Accountability

Mycovia Pharmaceuticals will provide the Investigator with sufficient amounts of IMP. It is the responsibility of the Investigator to ensure that a current record of inventory/IMP accountability is maintained.

6.6 Investigational Medicinal Product Return

Upon the completion or termination of the study, and with supporting documentation from Mycovia Pharmaceuticals (or designee), all unused and/or partially used IMP should be returned to Sponsor or its designee or destroyed at the investigational site per the site's standard operating procedure (SOP) for IMP destruction. Prior to destruction of any used or unused IMP at a site, Mycovia Pharmaceuticals (or designee) must review and provide written documentation that:

1. The site SOP for IMP destruction is acceptable.
2. The clinical site monitor has conducted and documented full accountability of the IMP.

7 TREATMENT OF SUBJECTS

7.1 Investigational Medicinal Product Administration and Dosing Schedule

7.1.1 Induction Phase (Screening/Randomization to Day 14)

At Screening all subjects will be randomized to receive 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 doses (every 72 hours) of over-encapsulated fluconazole 150 mg starting on Day 1

The number of capsules with active pharmaceutical ingredient (VT-1161 or fluconazole) and inactive capsules (placebo) for each treatment arm during the Induction Phase is described in Table 5.

Table 5. Number of Capsules Taken Per Treatment Group During Induction Phase

Treatment Group	Investigational Medicinal Product	Day 1 (# capsules)	Day 2 (# capsules)	Day 4 (# capsules)	Day 7 (# capsules)
VT-1161	VT-1161	4	3	0	0
	Placebo (Matching Fluconazole)	1	0	1	1
Fluconazole	Fluconazole	1	0	1	1
	Placebo (Matching VT-1161)	4	3	0	0

Regarding the dosing of fluconazole in adolescent subjects (12 to 17 years of age, inclusive), fluconazole exposure at the planned dose is anticipated to be similar to that in adults and proportional to weight. AEs associated with fluconazole would also be expected to be similar in adolescents as in adults. There are currently no United States FDA- or European-approved doses or regimens of fluconazole for treatment of VVC or RVVC in adolescents. While the United States FDA-approved labeling for fluconazole (Diflucan, Pfizer 2017) is silent on treatment of adolescents with VVC, the European prescribing information for fluconazole (Diflucan® Summary of Product Characteristics [2017]) provides the following guidance; "If treatment is imperative in adolescents (from 12 to 17 years old), the posology should be the same as in the adult population." Therefore, adolescent subjects (ages 12 to 17 years) enrolled in the study will receive the same 150 mg doses of fluconazole as adult subjects.

7.1.2 Maintenance Phase (Day 14 to Week 14)

Subjects returning to the site approximately 14 days after the first dose of VT-1161 or over-encapsulated fluconazole and demonstrating resolution of the VVC infection (defined by a signs and symptoms score of <3) will receive either:

- 150-mg once weekly dose of VT-1161 for 11 weeks, if initially randomized to receive VT-1161 or
- a matching placebo regimen for 11 weeks, if initially randomized to receive fluconazole.

Subjects will be instructed to take the doses of VT-1161 within 30 minutes after ingestion of the subject's main meal (as determined by the subject), at approximately the same time of the day consistently throughout the study. Subjects should consume approximately 240 mL (approximately 8 oz.) of water with each dose of IMP. Subject's Day 14 is defined as the first day of weekly dosing of IMP administration.

7.2 Method of Assigning Subjects to Treatment Groups

Each subject who completes the study Screening assessments, meets all eligibility criteria, and is accepted for the study will be assigned a unique sequential identification number and will receive the corresponding treatment according to the randomization scheme described in the Statistical Analysis Plan (SAP). For more information on subject randomization, see Section 7.7.

7.3 Dose Interruptions and Modifications

If any subject experiences a Grade 3 AE that is considered possibly related, or related to IMP, dosing will be discontinued in that subject and the AE will be followed until resolution (refer to Section 9.2 for AE reporting). Dosing of IMP will not be re-initiated in any subject who experiences a possibly related or related Grade 3 AE. Although these subjects should stop the study drug, they are encouraged to return for their remaining study visits. Elevation in laboratory values that do not require medical or surgical treatment or discontinuation from the study will not be considered AEs (Section 9.2.1).

If any subject experiences a Grade 4 AE that is considered possibly related or related to IMP, the subject may be unblinded at the discretion of the Mycovia Pharmaceuticals' Medical Monitor and Investigator and dosing of IMP will be discontinued, and the AE will be followed until resolution. Dosing of IMP will not be re-initiated in any subject who experiences a possibly related or related Grade 4 AE.

7.4 Prohibited and Permitted Medications/Non-Medications

All medications taken 30 days prior to the Screening visit including all prescription and non-prescription medications (e.g., herbal and/or vitamin supplements), through the End of Study (EOS) visit will be recorded for each subject.

All concomitant therapies and procedures (including any surgical and diagnostic procedures) that were performed 72 hours prior to Screening through the EOS visit will be recorded for each subject.

7.4.1 Prohibited Medications/Non-Medications

The following prescription and over-the-counter drug products are prohibited during the study and will be considered a protocol deviation:

1. Topical or oral antifungal drugs (with the exception of fluconazole when prescribed by the Investigator to treat a subject with a recurrent VVC episode. If subject fails to respond to fluconazole treatment, the Investigator may employ treatment options corresponding to us the site's standard of care treatment to treat the infection upon consult with the Medical Monitor.)

2. Topical products applied to the vulva or vagina (e.g. antibiotic, antitrichomonal, corticosteroids, or anti-inflammatory agents).

3. Oral antibacterial or antitrichomonal agents for the treatment of bacterial vaginosis, trichomonas, or other concomitant urogenital infection unless prescribed by the Investigator.

4. Oral or injectable corticosteroid or immunosuppressive drugs for the duration of the study. Use of topical (no vulvar or vaginal steroids), inhaled, ophthalmic, or intraarticular and intralesional steroids is permitted.

5. Drugs with a narrow therapeutic index that are metabolized by CYP3A4 and sensitive to the induction of CYP3A4 (carbamazepine, cyclosporine, fentanyl, quinidine, sirolimus and tacrolimus).

7.4.2 Permitted Medications/Non-Medications

The Investigator may prescribe a single dose of fluconazole to treat an acute VVC recurrence during the Maintenance Phase, when confirmed by a positive local KOH wet mount showing presence of yeast and clinical signs and symptoms score of ≥3.

Medications to treat any AEs the subject experiences during the study are permitted. If a subject is unable to comply with the excluded medications criteria (Section 7.4.1), the subject's continued participation in the study will be re-evaluated by the Investigator, in consultation with Mycovia Pharmaceuticals' Medical Monitor.

7.5 Treatment Compliance

IMP will be administered or dispensed only to eligible subjects under the supervision of the Investigator.

7.6 Replacement of Study Subjects

Any subject who receives ≥1 dose of study drug will be considered evaluable and will not be replaced.

7.7 Randomization and Blinding

A randomized design through an interactive web response system (IWRS) will be used to assign subjects in a 2:1 ratio to the dose regimen of VT-1161 or fluconazole and placebo. Day 1 (Screening) is defined as the first day of VT-1161/fluconazole administration and subsequent study days are defined by the number of consecutive days thereafter.

The subjects, study Investigators and their staff, all clinical staff members within Mycovia Pharmaceuticals, the clinical study monitor, the study project team, and the study Medical Monitor(s) will remain blinded to individual treatment assignments until the completion of the study. The Unblinded Statistician responsible for creating the final randomization list and the IWRS personnel responsible for loading the final randomization list into the IWRS will be unblinded to the treatments. The bioanalytical personnel responsible for assay of VT-1161 in plasma samples will also be unblinded to subject treatments.

7.8 Conditions for Breaking the Blind

In the event the breaking of the blind is required, the following will apply:

- The Investigator may unblind a subject's treatment assignment only in the case of an emergency (i.e., a Grade 4 AE) OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the Investigator (ICH GCP 4.3.1). If the SAE requires that an expedited regulatory report be sent to 1 or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to Investigators in accordance with local regulations.

- The Investigator must contact the Medical Monitor or appropriate Mycovia Pharmaceuticals study personnel to communicate the reasons for unblinding the subject's treatment assignment immediately after the unblinding occurred (ICH GCP 4.7).

- If unblinding is required, the Mycovia Pharmaceuticals' Medical Monitor and the Investigator will be provided with the treatment assigned to the subject. The Investigator must NOT disclose the treatment assignment to the subject and/or other study personnel including other site personnel, monitors, or the Sponsor's project team; nor should there be any written or verbal disclosure of the code in any of the corresponding subject documents. The treatment assignment of the subject is to be revealed only if that information is important to the safety of subjects currently in the study.

- The date and reason for unblinding must be fully documented in the eCRF.

7.9 Treatment After the End of the Study

After the completion of the study, Mycovia Pharmaceuticals will follow local regulatory/International Conference on Harmonisation (ICH) guidelines for any follow-up treatment provided to subjects. The Investigator is responsible for ensuring that consideration has been given to the post-study care of a subject's medical condition.

8 STUDY PROCEDURES

8.1 Assessments and Procedures

The study subjects should be seen within the timeframes noted in the Table 1. Schedule of Assessments and Procedures. All study visits should be scheduled within the visit windows and projected from the Screening (Day 1) visit.

Table 1. Schedule of Assessments and Procedures

Activities	Screening Day 1	Day 2[i]	Day 14 (±2 days) Initial TOC (±2	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 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 and 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: 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, AST, ALT, 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 to test 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 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 followed by 11 weekly doses of 150mg 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.

8.1.1 Screening (Day 1) Assessments and Procedures

The subject will be randomized and start IMP at Screening if the subject has met all preliminary enrollment criteria, (central lab results are not required to initiate IMP). Proper written informed consent or assent (for those ages 12-17) must be obtained from all subjects prior to any study procedures, see Section 13.2 for more information. Once the subject has signed the Institutional Review Board (IRB) approved informed consent document or assent the following evaluations will be performed to assess subject eligibility:

1. Review Inclusion and Exclusion criteria.
2. Document subject demographics, including date of birth, race, and ethnic origin.
3. Document and review medical/medication and surgical history, including all current, pertinent and major past illnesses and surgical procedures. All concomitant therapies or procedures (including any surgical or diagnostic procedures) that were performed 72 hours prior to the Screening will be recorded.
4. Review alcohol and tobacco history (previous 12 months).
5. Record all medications, including prescription and non-prescription medications, herbal products, and vitamin/mineral supplements taken within 30 days prior to Screening.
6. Assess height and weight to determine the body mass index.
7. Obtain vital signs in the sitting position (blood pressure, heart rate, respiratory rate, and temperature).
8. Conduct a comprehensive physical examination, including vaginal exam, as described in Section 9.1.3. For proper assessment, it is best the subject is not menstruating at time of the visit.
9. Recording of clinical signs and symptoms of vulvovaginitis, as outlined in Section 9.1.7. Subjects must be cautioned to not use any treatment (topical or systemic) for their infection during the Screening period.
10. KOH wet mount test, performed locally (Section 9.1.6).

11. Vaginal swab for culture will be obtained and sent to the central mycology laboratory (Section 9.1.6).

12. Standard 12-lead ECG will be obtained in the supine position (Section 9.1.4).

13. Clinical chemistries, hematology, and urinalysis for study eligibility as outlined in Section 9 and the Schedule of Assessments and Procedures. Cultures for testing of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* will also be taken. Vaginal pH will be determined. Local testing will be done for *Bacterial vaginosis* and an OSOM® Rapid test or similar test will be performed locally for *Trichomonas vaginalis*.

14. Testing for HBsAg, HCV, and HIV as outlined in Section 9.1.5.2 and the Schedule of Assessments and Procedures (results for these tests are not required for the start of the Induction Phase).

15. A urine pregnancy test will be performed locally and a serum pregnancy test will be obtained and sent to the central laboratory for all women of childbearing potential (WOCBP).

16. For subjects participating in intense PK sampling at participating sites, administer IMP within 30 minutes after a site-provided meal and 240 mL of water.

17. For subjects participating in intense PK sampling at participating sites, PK samples will be obtained pre-dose and at 1, 2, 4, and 8 hours after dosing. This is outlined in Section 10.1 and the Schedule of Assessments and Procedures.

18. IWRS randomization of the subject to a treatment arm.

19. Provide two bottles of IMP for **Induction Phase dosing** to subject along with dosing instructions.

20. Remind subjects that consented to intense PK sampling to return for Day 2 visit.

21. Remind subject that have NOT consented to intense PK sampling, to return for Day 14 visit.

Safety laboratory results are not required prior to start of treatment with IMP and mycology results will not be sent to sites. Subjects may be eligible for re-screening and the investigate

site is to refer to the Study Procedures Manual and contact the study clinical monitor for guidance.

8.1.2 Day 2 Assessments and Procedures – Intense PK Sampling

The subjects who have consented to intense PK sampling will return to the investigative site for the following evaluations:

1. Record all medications taken since the previous visit, including all prescription and non-prescription medications, herbal products, and vitamin/mineral supplements. All concomitant therapies or procedures (including any surgical or diagnostic procedures) that were performed since the last visit will be recorded.

2. Review and record any AEs.

3. Administration of IMP within 30 minutes after a site-provided meal and 240 mL water.

4. PK samples will be obtained pre-dose and at 1, 2, 4, and 8 hours after dosing. This is outlined in Section 10.1 and the Schedule of Assessments and Procedures.

5. Remind subject to return for Day 14 visit.

8.1.3 Day 14 (±2 Days) Assessments and Procedures

The subjects will return to the investigative site for the following evaluations:

1. Confirm all Inclusion and Exclusion criteria have been met

2. Record all medications taken since the previous visit, including all prescription and non-prescription medications, herbal products, and vitamin/mineral supplements. All concomitant therapies or procedures (including any surgical or diagnostic procedures) that were performed since the last visit will be recorded.

3. Review and record any AEs.

4. Obtain vital signs in the sitting position, (blood pressure, heart rate, respiratory rate, and temperature).

5. Limited physical examination, includes vaginal exam (as described in Section 9.1.3). For proper assessment, it is best the subject is not menstruating at time of the visit.

6. Recording of clinical signs and symptoms of vulvovaginitis, as outlined in Section 9.1.7. Subjects with clinical signs and symptoms score of < 3 will continue into Maintenance Phase and subjects with score of ≥3 will be an Induction failure, ending study participation. Subjects must be cautioned to not use any treatment (topical or systemic) for vulvovaginitis except study drug.

7. Vaginal swab for culture will be obtained and sent to the central mycology laboratory (Section 9.1.6).

8. Standard 12-lead ECG will be obtained in the supine position (Section 9.1.4).

9. Obtain PK plasma specimen.

10. Obtain clinical chemistries, hematology, and urinalysis as outlined in Section 9 and the Schedule of Assessments and Procedures.

11. Collect and review accountability of the two IMP **Induction Phase** bottles with the subject for compliance.

12. Dispense bottle for IMP **Maintenance Phase dosing (weekly)** to the subject along with instructions

13. Remind subject to return for Week 8 (±7 days) visit.

8.1.4 Week 8 (±7 Days) Assessments and Procedures

Subjects will return to the investigative site for follow-up evaluation as follows:

1. Record all medications taken since the previous visit, including all prescription and non-prescription medications, herbal products, and vitamin/mineral supplements. All concomitant therapies or procedures (including any surgical or diagnostic procedures) that were performed since the previous visit.

2. Review and record any AEs.

3. Obtain vital signs in the sitting position, (blood pressure, heart rate, respiratory rate, and temperature).

4. Limited physical examination, includes vaginal exam (as described in Section 9.1.3). For proper assessment, it is best the subject is not menstruating at time of the visit.

5. Recording of clinical signs and symptoms of vulvovaginitis, as outlined in Section 9.1.7. Subjects must be cautioned to not use any treatment (topical or systemic) for vulvovaginitis except study drug.

6. Vaginal swab for culture will be obtained and sent to the central mycology laboratory (Section 9.1.6).

7. Obtain clinical chemistries, as outlined in Section 9.1.5.3.

8. Review accountability of IMP **Maintenance Phase** bottle with the subject for compliance.

9. Remind subject to return for Week 14 (±14 days) visit.

8.1.5 Week 14 (±14 Days) Assessments and Procedures (End of Treatment)

The subjects will return to the investigative site for the following evaluations:

1. Record all medications taken since the previous visit, including all prescription and non-prescription medications, herbal products, and vitamin/mineral supplements. All concomitant therapies or procedures (including any surgical or diagnostic procedures) that were performed since the previous visit.

2. Review and record any AEs.

3. Obtain body weight.

4. Obtain vital signs in the sitting position, (blood pressure, heart rate, respiratory rate, and temperature).

5. Limited physical examination, includes vaginal exam (as described in Section 9.1.3). For proper assessment, it is best the subject is not menstruating at time of the visit.

6. Recording of clinical signs and symptoms of vulvovaginitis, as outlined in Section 9.1.7. Subjects must be cautioned to not use any treatment (topical or systemic) for vulvovaginitis except study drug.

7. Vaginal swab for culture will be obtained and sent to the central mycology laboratory (Section 9.1.6).

8. Standard 12-lead ECG will be obtained in the supine position (Section 9.1.4).

9. Obtain PK plasma specimen.

10. Obtain clinical chemistries, hematology, and urinalysis as outlined in Section 9 and the Schedule of Assessments and Procedures.

11. Obtain serum sample for pregnancy testing for all WOCBP.

12. Collect and conduct final review accountability of IMP **Maintenance Phase** bottle with the subject for compliance.

13. Remind subject to return for Week 20 (±14 days) visit.

8.1.6 Week 20 (±14 Days) Assessments and Procedures

The subjects will return to the investigative site for the following evaluations:

1. Record all medications taken since the previous visit, including all prescription and non-prescription medications, herbal products, and vitamin/mineral supplements. All concomitant therapies or procedures (including any surgical or diagnostic procedures) that were performed since the previous visit.

2. Review and record any AEs.

3. Obtain vital signs in the sitting position, (blood pressure, heart rate, respiratory rate, and temperature).

4. Limited physical examination, includes vaginal exam (as described in Section 9.1.3). For proper assessment, it is best the subject is not menstruating at time of the visit.

5. Recording of clinical signs and symptoms of vulvovaginitis, as outlined in Section 9.1.7. Subjects must be cautioned to not use any treatment (topical or systemic) for vulvovaginitis except study drug.

6. Vaginal swab for culture will be obtained and sent to the central mycology laboratory (Section 9.1.6).

7. Obtain clinical chemistries, as outlined in Section 9.1.5.3.

8. Remind subject to return for Week 26 (±14 days) visit.

8.1.7 Week 26 (±14 Days) Assessments and Procedures

Subjects will return to the investigative site for follow-up evaluations as follows:

1. Record all medications taken since the previous visit, including all prescription and non-prescription medications, herbal products, and vitamin/mineral supplements. All concomitant therapies or procedures (including any surgical or diagnostic procedures) that were performed since the previous visit.

2. Review and record any AEs.

3. Obtain body weight.

4. Obtain vital signs in the sitting position, (blood pressure, heart rate, respiratory rate, and temperature).

5. Limited physical examination, includes vaginal exam (as described in Section 9.1.3). For proper assessment, it is best the subject is not menstruating at time of the visit.

6. Recording of clinical signs and symptoms of vulvovaginitis, as outlined in Section 9.1.7. Subjects must be cautioned to not use any treatment (topical or systemic) for vulvovaginitis except study drug.

7. Vaginal swab for culture will be obtained and sent to the central mycology laboratory (Section 9.1.6).

8. Standard 12-lead ECG will be obtained in the supine position (Section 9.1.4).

9. Obtain clinical chemistries, hematology, and urinalysis as outlined in Section 9 and the Schedule of Assessments and Procedures.

10. Obtain serum sample for pregnancy testing for all WOCBP.

11. Remind subject to return for Week 32 (±14 days) visit.

8.1.8 Week 32 (±14 Days) Assessments and Procedures

Subjects will return to the investigative site for follow-up evaluations as follows:

1. Record all medications taken since the previous visit, including all prescription and non-prescription medications, herbal products, and vitamin/mineral supplements.

All concomitant therapies or procedures (including any surgical or diagnostic procedures) that were performed since the previous visit.

2. Review and record any AEs.

3. Obtain vital signs in the sitting position, (blood pressure, heart rate, respiratory rate, and temperature).

4. Limited physical examination, includes vaginal exam (as described in Section 9.1.3). For proper assessment, it is best the subject is not menstruating at time of the visit.

5. Recording of clinical signs and symptoms of vulvovaginitis, as outlined in Section 9.1.7. Subjects must be cautioned to not use any treatment (topical or systemic) for vulvovaginitis except study drug.

6. Vaginal swab for culture will be obtained and sent to the central mycology laboratory (Section 9.1.6).

7. Obtain clinical chemistries, as outlined in Section 9.1.5.3.

8. Remind subject to return for Week 38 (±14 days) visit.

8.1.9 Week 38 (±14 Days) Assessments and Procedures

Subjects will return to the investigative site for follow-up evaluations as follows:

1. Record all medications taken since the previous visit, including all prescription and non-prescription medications, herbal products, and vitamin/mineral supplements. All concomitant therapies or procedures (including any surgical or diagnostic procedures) that were performed since the previous visit.

2. Review and record any AEs.

3. Obtain vital signs in the sitting position, (blood pressure, heart rate, respiratory rate, and temperature).

4. Limited physical examination, includes vaginal exam (as described in Section 9.1.3). For proper assessment, it is best the subject is not menstruating at time of the visit.

5. Recording of clinical signs and symptoms of vulvovaginitis, as outlined in Section 9.1.7. Subjects must be cautioned to not use any treatment (topical or systemic) for vulvovaginitis except study drug.

6. Vaginal swab for culture will be obtained and sent to the central mycology laboratory (Section 9.1.6).

7. Obtain clinical chemistries, hematology, and urinalysis as outlined in Section 9 and the Schedule of Assessments and Procedures.

8. Remind subject to return for Week 44 (±14 days) visit.

8.1.10 Week 44 (±14 Days) Assessments and Procedures

Subjects will return to the investigative site for follow-up evaluations as follows:

1. Record all medications taken since the previous visit, including all prescription and non-prescription medications, herbal products, and vitamin/mineral supplements. All concomitant therapies or procedures (including any surgical or diagnostic procedures) that were performed since the previous visit.

2. Review and record any AEs.

3. Obtain vital signs in the sitting position, (blood pressure, heart rate, respiratory rate, and temperature).

4. Limited physical examination, includes vaginal exam (as described in Section 9.1.3). For proper assessment, it is best the subject is not menstruating at time of the visit.

5. Recording of clinical signs and symptoms of vulvovaginitis, as outlined in Section 9.1.7. Subjects must be cautioned to not use any treatment (topical or systemic) for vulvovaginitis except study drug.

6. Vaginal swab for culture will be obtained and sent to the central mycology laboratory (Section 9.1.6).

7. Obtain clinical chemistries, as outlined in Section 9.1.5.3.

8. Remind subject to return for Week 50 (±14 days) visit.

8.1.11 Week 50 (±14 Days) Assessments and Procedures (End of Study)

Subjects will return to the investigative site for follow-up evaluations as follows:

1. Record all medications taken since the previous visit, including all prescription and non-prescription medications, herbal products, and vitamin/mineral supplements. All concomitant therapies or procedures (including any surgical or diagnostic procedures) that were performed since the previous visit.
2. Review and record any AEs.
3. Obtain body weight.
4. Obtain vital signs in the sitting position, (blood pressure, heart rate, respiratory rate, and temperature).
5. Limited physical examination, includes vaginal exam (as described in Section 9.1.3). For proper assessment, it is best the subject is not menstruating at time of the visit.
6. Recording of clinical signs and symptoms of vulvovaginitis, as outlined in Section 9.1.7. Subjects must be cautioned to not use any treatment (topical or systemic) for vulvovaginitis except study drug.
7. Vaginal swab for culture will be obtained and sent to the central mycology laboratory (Section 9.1.6).
8. Standard 12-lead ECG will be obtained in the supine position (Section 9.1.4).
9. Obtain PK plasma specimen.
10. Obtain clinical chemistries, hematology, and urinalysis as outlined in Section 9 and the Schedule of Assessments and Procedures.
11. Obtain serum sample for pregnancy testing for all WOCBP.

If the Investigator suspects the subject is experiencing a recurrent episode at a regular study visit, a local KOH wet mount test is to be performed to confirm whether filamentous hyphae/pseudohyphae and/or budding yeast cells are present.

8.1.12 Unscheduled Visit Assessment and Procedures

Subjects should be encouraged to return for an unscheduled visit if they experience a recurrence of VVC anytime during the study. The following evaluations are to be performed:

1. Record all medications taken since the previous visit, including all prescription and non-prescription medications, herbal products, and vitamin/mineral supplements. All concomitant therapies or procedures (including any surgical or diagnostic procedures) that were performed since the previous visit.

2. Review and record any AEs.

3. Obtain vital signs in the sitting position, (blood pressure, heart rate, respiratory rate, and temperature).

4. Limited physical examination, includes vaginal exam (as described in Section 9.1.3). For proper assessment, it is best the subject is not menstruating at time of the visit.

5. Recording of clinical signs and symptoms of vulvovaginitis, as outlined in Section 9.1.7. Subjects must be cautioned to not use any treatment (topical or systemic) for vulvovaginitis except study drug.

6. KOH wet mount test, performed locally (Section 9.1.6).

7. Vaginal swab for culture will be obtained and sent to the central mycology laboratory (Section 9.1.6).

8. Obtain clinical chemistries, as outlined in Section 9.1.5.3.

If a subject has a recurrent acute VVC episode prior to the end of treatment at Week 14, the subject will continue her assigned treatment through Week 14 and will receive one dose of fluconazole to treat her acute VVC infection. Throughout the Maintenance Phase, the Investigator is to prescribe one dose of fluconazole to treat the acute VVC episode, once confirmed by a positive KOH to show presence of yeast and if the clinical signs and symptoms score is ≥3. If subject fails to respond to fluconazole treatment, the Investigator may employ treatment options corresponding to the site's standard of care treatment to treat the infection upon consult with the Medical Monitor.

If a subject comes in for an unscheduled visit to repeat a procedure (i.e., ECG, safety labs, etc.), only those specific procedures need to be performed, along with collection of any changes in medical treatments, medications and collection of any AEs.

If subjects experience any AEs other than a potential recurrent VVC episode they may be evaluated at the site at the Investigators discretion.

8.2 Exercise

Subjects will be encouraged, if possible, to avoid engaging in strenuous activity within 48 hours prior to study visits. Walking at a normal pace during these periods is acceptable.

9 SAFETY ASSESSMENTS

9.1 Safety Tests and Assessments

Safety assessments will include attention to relevant changes in the following parameters, which are identified as occurring after the start of IMP, regardless of whether the change is in an examination finding, test result, or symptom(s) reported by a subject, and regardless of presumed relationship to IMP (VT-1161 or fluconazole and placebo). The Investigator will follow all clinically significant abnormal findings after IMP treatment until resolution, return to baseline, or permanent documented change in medical history.

9.1.1 Height and Weight

Height and body weight will be collected at times specified in Table 1. Schedule of Assessments and Procedures.

9.1.2 Vital Signs

Vital signs to include body temperature, heart rate (pulse), breathing rate, and blood pressure will be obtained in a sitting position after resting for at least 5 minutes at times specified in Table 1. Schedule of Assessments and Procedures.

9.1.3 Physical Examination

Comprehensive Physical Examination: general appearance; head, eyes, ears, nose, and throat; thyroid/neck (endocrine); chest and lungs; cardiovascular system, abdomen, pelvic exam, musculoskeletal system, lymph nodes, extremities/skin, and neurological system will be performed at Screening. Special attention should be given during the vulvovaginal examination to erythema, edema, and excoriation. For proper assessment, it is best the subject is not menstruating at time of the study visits.

Symptom Directed Physical Examination: A symptom directed physical exam consists of a very brief history of present illness. Investigators should use the symptom directed exam for all study visits after the Screening visit. If the subject has no present illness this should be documented by the Investigator or qualified designee.

9.1.4 Electrocardiograms

Standard 12-lead ECGs to assess heart rate, rhythm, and interval information such as PR, QRS, QT, and QTc will be obtained in the supine position at times specified in Table 1. Schedule of Assessments and Procedures.

9.1.5 Laboratory Determinations

After the Screening (Day 1) visit, laboratory test values that fall outside the reference range on the laboratory reports and are deemed clinically significant by the Investigator may be repeated at the discretion of the Investigator. Those values deemed clinically significant should be followed until resolution or permanent documented change in medical history.

The following laboratory samples will be obtained at times specified in the Schedule of Assessments and Procedures and analyzed by the central laboratory:

9.1.5.1 Pregnancy Testing

All WOCBP must undergo urine and serum pregnancy testing at Screening to assess protocol eligibility. Serum pregnancy tests will be performed thereafter as specified in the Schedule of Assessments and Procedures.

9.1.5.2 Immunology

HIV antibody, HBsAg, anti-HCV at Screening. Laboratory results are not required prior to start of IMP. Investigators are to follow local and/or state laws in regards to parental disclosure of any positive pregnancy tests or reportable and treatable serologies or STDs in adolescents.

9.1.5.3 Clinical Chemistry Panel

Creatinine, blood urea nitrogen, AST, ALT, alkaline phosphatase, total bilirubin, conjugated bilirubin, albumin, total protein, total carbon dioxide, glucose, sodium, potassium, chloride, calcium, phosphorus, CK, cholesterol and triglycerides. Testing for HbA1c should be performed in known or suspected diabetic subjects at Screening. Laboratory results are not required prior to start of IMP.

After the Screening (Day 1) visit, subjects may be re-tested for ALT, AST and total bilirubin to confirm any abnormal values and to determine if they are increasing or decreasing. The Investigator will also assess the subject for any associated emergent symptoms.

9.1.5.4 Hematology

A complete blood count with differential to include red blood cell count, total and differential white blood cell counts, hemoglobin, hematocrit, RBC, MCV, MCH, MCHC, RDW and platelet count will be performed at times specified in Table 1. Schedule of Assessments and Procedures. Laboratory results are not required prior to start of IMP.

9.1.5.5 Urinalysis

Testing for glucose, ketones, leukocyte esterase, nitrite, blood, pH, protein, and specific gravity will be performed at times specified in Table 1. Schedule of Assessments and Procedures. Laboratory results are not required prior to start of IMP.

9.1.5.6 Chlamydia Trachomatis and Neisseria Gonorrhoeae

Cultures to test for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* will be taken at Screening.

9.1.5.7 Trichomonas Vaginalis

An OSOM® Rapid test or similar test will be performed for *Trichomonas vaginalis* locally at Screening. Instructions for collecting, processing, storing, and shipping samples to the central laboratory are outlined in the laboratory manual. Testing for *Bacterial vaginosis* will be done locally.

9.1.6 KOH Wet Mount Tests and Fungal Cultures

A local KOH wet mount test will be performed locally at the Screening visit and at unscheduled visits where a recurrent VVC episode is suspected. A vaginal fungal culture will be obtained at Screening and all subsequent visits and sent to the central mycology laboratory for fungal identification and susceptibility testing according to approved Clinical Laboratory Standards Institute methods. Subjects should not be menstruating at time of the study visits to ensure proper sample collection of the vaginal fluid. Details as to the collection of samples, shipping, testing methods and analysis will be delineated in a laboratory manual. Mycology samples may be retained for future analysis for a period of up to 15 years, after which time the samples will be destroyed.

9.1.7 Vulvovaginitis Clinical Assessment

Vulvovaginal signs and symptoms will be evaluated at Screening and each subsequent study visit. Each of the following vulvovaginal signs and symptoms will be scored and the individual scores combined for a maximum score of 18, using the following scale:

a. Signs: erythema, edema, and excoriation
b. Symptoms: itching, burning, and irritation

Scoring Scale: Each score should be objectively defined on a scale of 0 to 3 as follows:

0 = none (complete absence of any signs or symptoms)

1 = mild (slight)

2 = moderate (definitely present)

3 = severe (marked, intense)

9.2 Adverse Event Reporting

9.2.1 Definition of Adverse Events

Monitoring of all AEs will be conducted throughout the study as specified in the Schedule of Assessments and Procedures.

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 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 during the study.

Any abnormal safety assessments, such as ECGs, radiological scans, vital sign measurements, that are judged by the Investigator to be clinically significant should be recorded as an AE or SAE provided it meets one of those definitions. 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) that is independent from a known underlying medical condition and that requires medical or surgical intervention, or leads to IMP interruption or discontinuation, should be considered an AE.

Clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied are not considered AEs unless their severity is greater than expected in the judgement of the Investigator.

In addition, the following apply:

- All AEs, including clinically significant laboratory abnormalities, will be documented as an AE and followed until resolution.

- All AEs and SAEs will be collected from the start of taking the first dose of IMP until the last follow-up visit of the study, at the time points specified in the Schedule of Assessments and Procedures.

- Medical occurrences that begin prior to the start of IMP but after obtaining informed consent or assent (for those ages 12-17) should be recorded in the medical history section of the eCRF.

- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the Investigator learns of an SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the Investigator must promptly notify Mycovia Pharmaceuticals.

9.2.2 Definition of a Serious Adverse Event

An SAE is any AE occurring after the first administration of IMP that results in any of the following outcomes:

- Death[a]

- Is a life-threatening experience[b]

- Requires inpatient hospitalization or prolongation of existing hospitalization

- Results in a persistent or significant disability/incapacity[c]

- Results in a congenital anomaly/birth defect

- Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed above. Example: allergic bronchospasm requiring intensive treatment in an emergency room or at home.

NOTES:

a. "Death" is an outcome and is NOT the AE. In the event of death, the cause of death should be recorded as the SAE. The only exception is "sudden death" when the cause is unknown.

b. Life-threatening SAEs include any adverse drug experience, which, in the view of the Investigator, places the subject at immediate risk of death from the reaction as it occurs. It does not include a reaction that, had it occurred in a more serious form, might have caused death.

c. Disability is defined as a substantial disruption in a person's ability to conduct normal life functions.

All SAEs, regardless of causal relationship, must be reported to Mycovia Pharmaceuticals (or designee) within 24 hours of the site's knowledge of the event. The initial report must be captured in the electronic SAE CRFs within 1 business day.

The SAE report should provide as much of the required information as is available at the time. The following minimum information is required for reporting an SAE: subject identification number, reporting source, and an event outcome. Supplemental information may be entered into the electronic SAE CRFs and should not delay the initial report. Mycovia Pharmaceuticals (or designee) may contact the investigational site to solicit additional information or to follow-up on the event.

If there is any doubt whether the information constitutes an SAE, the information will be treated as an SAE for the purposes of this protocol.

All SAEs will be followed until resolution, return to baseline (when worsening of a pre-existing condition is reported), or permanent documented change in medical history.

All relevant documentation pertaining to the SAE (additional laboratory tests, consultation reports, discharge summaries, post-mortem reports, etc.) will be provided by the Investigator to Mycovia Pharmaceuticals (or designee) in a timely manner.

9.2.3 Recording of Adverse Events

Subjects should be instructed to report all AEs to the Investigator. In addition, the Investigator should seek to elicit any clinical or objective reactions by open-ended questioning ("How have you been feeling?") and, as appropriate, by examination. All AE information obtained during the subject questioning should be documented in the subjects' clinical records and entered into the CRF. All clearly related signs, symptoms, and results of diagnostic procedures performed because of an AE should be grouped together and recorded as a single diagnosis. The component parts of the diagnosis may be listed for verification. If the AE is a laboratory abnormality that is part of a clinical condition or syndrome, it should be recorded as the

syndrome or diagnosis rather than the individual laboratory abnormality. It should also be documented, verbatim, directly on the laboratory report.

To avoid vague, ambiguous, or colloquial expressions, all AEs should be recorded in standard medical terminology on the CRF and on the medical record rather than in the subject's own words. Each AE will also be described in terms of duration (start and stop date), severity, association with the IMP, action(s) taken, and outcome.

9.2.4 Severity of Adverse Events

All AEs and SAEs will be assessed by the Investigator or MD designee for severity, according to the Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table, (Draft, November 2007) Appendix A. For AEs involving a body system or laboratory value which is not addressed in the DMID Adult Toxicity Table, the most recent version of the Common Terminology Criteria for Adverse Events, version 4.0 published by the National Cancer Institute will be used.

Where discrepancies in the ULN and lower limit of normal (LLN) laboratory ranges occur between those included in the DMID and those of the central laboratory that performs the assays, the values provided by the central laboratory will be used for assignment of severity grade.

For AEs involving a body system or laboratory value not addressed in the DMID Adult Toxicity Table, the following general scale may be used with Investigator discretion to assign severity:

- **GRADE 1 Mild**: An event easily tolerated by the subject; transient or mild discomfort (usually < 48 hours); no medical intervention/therapy required.
- **GRADE 2 Moderate**: An event that may interfere with normal, everyday activities; some assistance may be needed; no or minimal medical intervention/therapy required.
- **GRADE 3 Severe**: An event that prevented the subject from performing their normal, everyday activities; some assistance usually required; medical intervention/therapy required; hospitalizations possible.
- **GRADE 4 Life-threatening**: At the time of the event the subject was at risk of death or the event resulted in a persistent or significant disability or incapacity.

- **GRADE 5 Death**: An event that resulted in death.

When changes in the severity of an AE occur more frequently than once a day, the maximum severity for the experience that day should be noted. If the severity category changes over several days, then those changes should be recorded separately (with distinct onset dates).

NOTE: An AE that is assessed as severe should not be confused with an SAE. Severity is a category utilized for rating the intensity of an event (such as mild, moderate, or severe myocardial infarction). However, the event itself may be of relatively minor medical significance, (such as a severe headache), and both AE(s) and SAE(s) can be assessed as severe. An event is defined as 'serious' when it meets one of the pre-defined outcomes as described in Section 9.2.2.

Where discrepancies in the ULN and lower limit of normal of laboratory ranges occur between those included in the DMID tables and those of the central laboratory that performs the assays, the values provided by the central laboratory will be used for assignment of severity grade.

9.2.5 Causality Assessment

The Investigator is obligated to assess the relationship between the IMP and the occurrence of each AE or SAE by using his or her best clinical judgment. It should be clearly documented in the medical notes that he/she has reviewed the AE/SAE and that they are the ones providing the assessment of causality. Other elements to be considered, such as the history of the underlying disease, concomitant therapy, other risk factors, and the temporal relationship of the event to the IMP will be considered and investigated. The Investigator will also consult the VT-1161 Investigational Brochure and the study Medical Monitor in estimating the relationship.

An SAE may be recorded when the Investigator has minimal information to include in the initial report. However, the Investigator must always make an assessment of causality for every event prior to reporting the SAE report. The Investigator may change his or her opinion of the causality upon evaluation of follow-up information or discussions with the study Medical Monitor with subsequent amendment of the SAE report. ***Causality assessment is one of the criteria used to determine regulatory reporting requirements and should not be left blank.***

For each reported adverse reaction, the Investigator must assess the relationship of the event to the IMP using the following scale:

Unrelated:

- Does not follow a known response pattern to the suspect IMP (if response pattern is previously known).
- Can clearly be explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

Unlikely Related:

- The temporal sequence from administration of the IMP suggests that a relationship is unlikely.
- Follows a response pattern that is unlike that of the suspect IMP (if response pattern is previously known).
- Could be reasonably explained by the subject's clinical state or other modes of therapy administered to the subject.

Possibly Related:

- Follows a reasonable temporal sequence from administration of the IMP.
- May follow a known response pattern to the suspect IMP (if response pattern is previously known).
- Could also be reasonably explained by the subject's clinical state or other modes of therapy administered to the subject.

Related:

- Follows a reasonable temporal sequence from administration of the IMP.
- Could not be reasonably explained by the known characteristics of the subject's clinical state or any other modes of therapy administered to the subject.
- Is confirmed by improvement on stopping or slowing administration of the IMP, if applicable.

If an assessment is not provided, the event will be treated as Possibly Related for purposes of regulatory reporting.

9.2.6 Action Taken Following Adverse Events

For each reported AE and SAE, the Investigator must document the action taken according to the following criteria:

- No action taken
- Non-pharmacologic treatment added
- New drug therapy added
- IMP interrupted
- Discontinued from study
- New or prolonged hospitalization

9.2.7 Outcome of Adverse Events

For each reported AE and SAE, the Investigator must document the outcome according to the following criteria:

- Resolved
- Ongoing
- Unknown
- Death

The appropriate AE or SAE report page will be updated once the outcome is determined. The Investigator will also ensure that additional follow-up information includes any supplemental data that may explain causality of the event(s).

For SAEs, new or updated information will be recorded on the originally completed SAE report, with all changes signed and dated by the Investigator or designee. The updated SAE report will then be signed by the Investigator and resubmitted to Mycovia Pharmaceuticals (or designee).

9.2.8 Other Reportable Events

Reports of overdose (with or without an AE), abuse, dependency, inadvertent or accidental exposure, pregnancy and unexpected therapeutic benefit should be forwarded to Mycovia Pharmaceuticals (or designee) in the same time frame as an SAE.

Overdose occurs when a subject is administered or has taken a dose substantially greater than the intended or scheduled dose specified by the protocol.

All pregnancies occurring from the time the subject takes their first dose of IMP through the last study visit (Week 50) must be followed for information regarding the course of pregnancy, delivery, and condition of the newborn. Follow-up should be provided by the Investigator to Mycovia Pharmaceuticals in a timely manner.

10 PHARMACOKINETIC ASSESSMENTS

10.1 Sample Collection and Handling

Blood samples for determination of VT-1161 plasma concentrations will be collected at visits specified in Schedule of Assessments and Procedures. Timing of samples will be with respect to the day and time study drug is administered. Intense PK blood draws for VT-1161 plasma concentrations will be obtained from consenting subjects, at participating sites, on Day 1 and Day 2, (predose and 1, 2, 4, and 8 hours after dosing, with ±10-minute window per timepoint). The date and time of each PK sample will be recorded in the CRF. PK samples should be stored frozen at -20°C or colder. Detailed shipping instructions will be provided in the lab manual.

10.2 Analytical Procedures

Plasma samples will be analyzed to determine concentrations of VT-1161 using a validated, specific and sensitive liquid chromatography/tandem mass spectrometry method at a bioanalytical laboratory designated by Mycovia Pharmaceuticals. Pharmacokinetic samples may be retained for future analysis of the metabolite profile for a period of up to 15 years, after which time the samples will be destroyed.

10.3 Pharmacokinetic Parameters

For subjects in the VT-1161 treatment arm, VT-1161 concentrations will be presented by visit with descriptive statistics. The PK data may be used in a cross-population PK analysis that may be presented in a separate report.

11 STUDY TERMINATION AND SUBJECT DISCONTINUATION

11.1 Screening/Baseline Failures

Subjects who sign and date the informed consent form or assent (for those ages 12-17) but fail to be randomized are defined as screen failures. Site personnel should maintain documentation for all subjects who sign an informed consent or assent. Study completion is defined as when the last subject has completed their last study visit.

11.2 Subject Withdrawal or Premature Discontinuation from the Study

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The incidence or severity of AEs in the study indicates a potential health hazard to subjects.
- The site must attempt to contact the subject and reschedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow-up', the Investigator or designee must make every effort to regain contact with the subject (e.g., multiple telephone calls on various dates/time, a certified letter to the subject's last known mailing address, or equivalent methods). These contact attempts should be documented in the subject's source documents.
- Should the subject continue to be unreachable, only then will they be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

A subject may be withdrawn due to lack of tolerability or safety concerns, including study drug-related AEs or development of clinically-significant study drug-related laboratory abnormalities. If a subject is withdrawn from treatment, the subject must be followed clinically until the event is resolved or deemed stable. A subject must be discontinued from the study drug if ALT or/and AST is > 5 times the upper limit of normal (ULN) or ALT or/and AST is > 3 times the ULN and serum total bilirubin is > 2 times the ULN.

A subject may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or administrative reasons. If a subject withdraws from the study, he/she may request destruction of any laboratory samples taken, and the Investigator must document this in the site study records and communicate this request to Mycovia Pharmaceuticals.

Subject who want to discontinue from the study should be encouraged to remain in the study for all remaining visits through Week 50 for safety and efficacy assessments. All subjects who do discontinue early from the study should have all EOS procedures performed on the day of discontinuation.

If a subject is prematurely discontinued from study treatment for any reason other than withdrawal of consent, the Investigator (or designee) should request that the subject continues to participate in the study, attending all remaining visits in accordance with the Schedule of Assessments and Procedures. Subjects who prematurely discontinue study medication, but remain in the study, may be treated according to the standard local practice. If the subject does not agree to remain in the study, the Investigator (or designee) must make every effort to perform the early withdrawal visit/EOS visit procedures.

11.3 Subject and Study Completion

A completed subject is one who has completed all visits, Screening through Week 50 (EOS), as defined in the Schedule of Assessments and Procedures. Study completion is defined as when the last subject has completed their last study visit.

11.4 Premature Study Termination

Reasons for discontinuation of the study at the investigative site may include, but are not limited to, the following:

- The incidence or severity of AEs in the study indicates a potential health hazard to subjects.
- Subject wishes to withdraw consent for reasons other than an AE.
- Subject non-compliance or unwillingness to comply with the procedures required by the protocol.
- Investigator request to withdraw from participation.
- Sponsor decision.
- Serious and/or persistent non-compliance by the Investigator with the protocol, the clinical research agreement, the Form Food and Drug Administration 1572, or applicable regulatory guidelines in conducting the study.
- Decision by the IRB/IEC to terminate or suspend approval for the investigation or the Investigator.
- Investigator fraud (altered data, omitted data, or manufactured data).

12 STATISTICAL ANALYSIS

A formal SAP will be finalized before 50% of subjects are enrolled. The SAP will provide a more technical and detailed description of the proposed data analysis methods and procedures. Any deviation from the analyses outlined in the protocol will be described in the SAP.

The primary statistical objectives of this study are:

1. To determine if there is a difference in the proportions of subjects with one or more episodes of culture-verified acute VVC in those receiving VT-1161 compared to those receiving placebo; and

2. To determine if there is a difference in the ability of VT-1161 and fluconazole to resolve acute episodes in RVVC subjects.

12.1 Determination of Sample Size

The study will enroll 180 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 subjects in the VT-1161 arm and 41 subjects in the fluconazole/placebo arm provides at least 90% power to detect a treatment difference between the VT-1161 treatment group and the fluconazole / placebo treatment group with a type 1 error rate of 0.05. (PASS 2008: Fisher's exact test, two-sided alpha = 0.05, and assuming 50% of 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).

12.2 Analysis Populations

ITT Population: All randomized subjects.

Safety Population: All randomized subjects who received at least 1 dose of IMP.

PP Population: All randomized subjects who had the following:

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

Modified ITT: All randomized subjects who had the following:

- Positive KOH at Screening.
- Positive culture at Screening.
- Negative culture at Baseline.

All statistical populations will be defined in the SAP.

12.3 Missing Data

For the efficacy analyses, missing values for the Investigator's assessment of clinical signs and symptoms or the culture result 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. The procedure PROC MI in SAS will be used to generate 10 possible imputed datasets.

Multiple sensitivity analyses will be performed for the primary endpoint to assess the impact of missing data on the results. The details of these sensitivity analyses will be outlined in the SAP.

12.4 Multiple Testing

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. [redacted]

[redacted]

12.5 Demographic and Baseline Characteristic Analyses

Subject disposition, demographics, baseline characteristics and study drug exposure will be summarized by treatment group.

12.6 Efficacy Analyses

Clinical and mycological assessments will be conducted as outlined in the Schedule of Assessments and Procedures.

The primary efficacy outcome measure is the proportion of subjects with one or more culture-verified acute VVC episodes (post-randomization through Week 50) in the ITT population, which will include the subjects who failed clearing their infection during the Induction Phase. 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. The primary efficacy outcome will be analyzed with a chi-square test. The Wilson-Hiferty transformation will be applied to the Chi-square test statistics prior to combining the 10 results using PROC MIANALYZE.

The key secondary efficacy outcome measures include the following:

- 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 of ≥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* during the Maintenance Phase.

The secondary endpoint of the proportion of subjects with resolved acute VVC infections at Day 14 in the VT-1161 arm will be evaluated for non-inferiority versus the fluconazole arm. 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.

Justification of the non-inferiority margin: Fluconazole clears 80% of acute VVC infections. Women can clear a VVC infection without intervention only when the infection is mild and even then, the complete clearance of the infection is very rare. Thus, a conservative estimate for the effect of fluconazole to treat a VVC infection versus no intervention is at least 70% (assuming 10% clear with no intervention). Per the FDA guidance document on Non-Inferiority Clinical Trials to Establish Effectiveness, a non-inferiority margin that is half the effect of the control drug should be used. A non-inferiority margin of 15% was selected for this trial which is equivalent to approximately 21% of the effect of fluconazole, which is substantially less than the recommended use of 50% of the effect of the control drug for the non-inferiority margin.

The secondary endpoints of the proportion of subjects with at least one culture-verified acute VVC episode during the Maintenance phase, and the proportion of subjects with at least one positive culture for *Candida* during the Maintenance phase, will be analyzed using a similar method as the primary efficacy outcome. The secondary endpoint of time to first recurrence will be analyzed using the Kaplan-Meier method. Subject's with no recurrence will be

censored at their last non-missing assessment. Differences between treatment groups will be assessed using a log-rank test.

Subject who want to discontinue from the study should be encouraged to remain in the study for all remaining visits through Week 50 for safety and efficacy assessments. Subjects who do discontinue early from the study should have all Week 50/EOS assessments performed on the day of discontinuation.

12.7 Safety Analyses

To meet the safety dataset requirement, approximately 150 subjects will be screened to randomize approximately 180 subjects that would meet the inclusion/ exclusion criteria. Assuming a 20% discontinuation rate, it is expected that approximately 144 subjects will complete the study.

All subjects who receive at least one dose of IMP will be included in the safety analyses. Subjects will be analyzed as per the treatment they receive. The number and percentage of subjects having TEAEs will be tabulated by system organ class and preferred term with a breakdown by treatment group. Mean changes from pre-treatment in vital signs, ECGs, and clinical laboratory variables will be summarized by treatment group.

AEs will be collected from the date of the first dose of IMP through Week 50 (EOS). Physical examination findings, vital signs, ECGs and safety laboratory tests (hematology and chemistry) will be obtained throughout the study as outlined in the Schedule of Assessments and Procedures. All concomitant medications taken during the period from 30 days prior to Screening through the Week 50 (EOS) visit will be recorded in the CRF. Pertinent and all major medical conditions will be recorded on the Medical History CRF.

For subjects discontinuing early from the study, every effort will be made for all EOS procedures to be performed as outlined in the Schedule of Assessments and Procedures. AEs will be coded with the Medical Dictionary for Regulatory Activities (MedDRA®) version 21 dictionary, or higher. The number and percentage of subjects having treatment-emergent AEs will be tabulated by system organ class and MedDRA® preferred term with a breakdown by treatment group. Mean changes from pre-treatment in vital signs, ECG, and clinical laboratory variables will be summarized by treatment group. The AE profile will be characterized with severity and relationship to IMP. SAEs and AEs resulting in discontinuation of IMP will be identified.

Treatment-emergent abnormal laboratory test results will be identified. Treatment-emergent abnormal laboratory tests results are those in which the baseline value is within normal laboratory limits and at least 1 post-baseline value is outside normal laboratory limits. Baseline will be defined as the last clinical laboratory result obtained before the first dose of IMP. Per protocol, the baseline for laboratory values should be obtained at the Screening (Day 1) visit.

Change from baseline to the minimum, maximum, and final vital sign value after first dosing will be summarized descriptively.

ECG measurements will include heart rate, QT interval, QTc interval, PR interval, and QRS interval. Baseline for ECG measurements is defined per protocol as the value pre-dosing at the Day 1 (Baseline) visit. Change from baseline will be summarized descriptively at each scheduled evaluation. Subjects with clinically significant changes in ECG rhythm or waveform will be identified. Subjects who meet each of the following criteria from ICH 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 identified.

- QT or Fridericia-corrected QT >450 msec
- QT or Fridericia-corrected QT >480 msec
- QT or Fridericia-corrected QT >500 msec
- QT or Fridericia-corrected QT increases from baseline by at least 30 msec
- QT or Fridericia-corrected QT increases from baseline by at least 60 msec

12.8 Pharmacokinetic Analyses

For subjects in the VT-1161 treatment arms, VT-1161 concentrations will be presented by visit with descriptive statistics. The PK data may be used in a cross-population PK analysis that may be presented in a separate report.

13 CLINICAL STUDY ADMINISTRATION/STUDY GOVERNANCE CONSIDERATIONS

13.1 Ethical Conduct of Study

The study will be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, the guiding principles of the current version of the Declaration of Helsinki, and applicable country-specific regulatory requirements. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments, as applicable, informed consent documents or assents (for those ages 12-17), and investigational brochure.
- Signed informed consent form or assent to be obtained for each subject before participation in the study (and for amendments as applicable).
- Investigator reporting requirements (e.g., continuing reviews, reporting of AEs/SAEs/protocol deviations to the IRB/IEC).
- If any documents are translated, an official certificate of translation must be maintained.

13.2 Informed Consent or Assent

Written informed consent or assent (for those ages 12-17) must be obtained from all subjects. The informed consent or assent document must be signed and dated prior to the initiation of study-related tests and prior to administration of IMP. The original signed informed consent or assent for each participating subject shall be filed with records kept by the Investigator(s). A copy of the informed consent or assent document must be provided to the subject. If applicable, it will be provided in a certified translation of the local language.

13.3 Quality Control (Study Monitoring)

In accordance with applicable regulations, including GCP, the representative(s) or the designated clinical study monitor of Mycovia Pharmaceuticals will contact the site staff prior to the start of the study to review the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and Mycovia Pharmaceuticals' requirements. When reviewing the data collection procedures, the discussion will also include identification, agreement, and documentation of data items that will serve as the source document.

Mycovia Pharmaceuticals representative(s) or the designated clinical study monitor will monitor the study and site activity at regular intervals throughout the study to verify the following:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The Investigator and the head of the medical institution (where applicable) agrees to allow the clinical study monitor direct access to all relevant documents.

Relevant documents or source documents are defined as the results of original observations and activities of a clinical investigation. Source documents may include, but are not limited to, study progress notes, e-mail correspondences, computer printouts, laboratory data, and drug accountability records.

13.4 Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, Mycovia Pharmaceuticals may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after the completion of the study. In the event of an assessment, audit or inspection, the Investigator (and institution) must agree to grant the advisor(s), auditor(s), and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues, and to implement any corrective and/or preventative actions to address any findings/issues identified.

13.5 Compliance with Standards of Medical Research/ Deviations

This protocol will be conducted in accordance with the applicable ICH guidelines and GCP. Any instance of non-compliance with the protocol will result in a documented deviation. If a change is deemed necessary to protect the safety, rights or welfare of a subject, Mycovia Pharmaceuticals and IRB/IEC should be notified as soon as possible and preferably prior to introducing the deviation. Major deviations are defined as, but not limited to, the following:

- Subjects who did not meet entry criteria.

- Subjects who developed withdrawal criteria during the study but were not withdrawn.
- Subjects who received the wrong treatment or incorrect dose.
- Subjects who were <80% IMP compliant in the Induction phase or <50% IMP compliant in the Maintenance Phase.
- Subjects who received an excluded concomitant medication or treatment.

13.6 Data Management

Electronic case report forms (eCRFs) will be used to capture study results and data. The study coordinator or other authorized site study personnel will transcribe data from source documents into the eCRFs. All eCRFs will be reviewed and source verified by the clinical study monitor during periodic site visits, and the clinical study monitor will ensure that all data in the eCRF are correct and complete. Prior to or between visits, the Medical Monitor or clinical study monitor may request copies of the eCRFs for preliminary medical review. Once the eCRFs are complete and source verified, the Investigator must sign and date all required pages, verifying the accuracy of all data contained within the eCRF.

Training will be provided for the Electronic Data Capture (EDC) system. All personnel using the EDC system must have the appropriate education, training, and experience, or any combination thereof. The Investigator will be provided with SOPs (contained in the Study Procedures Manual or a vendor-specific SOP) on the use of the EDC system. Documentation for employee education, training, and previous experience that pertains to the EDC system must be present in the Investigator files.

If electronic data systems other than those provided and maintained by Mycovia Pharmaceuticals are used for documentation and data capture, the Investigator must ensure that the systems are validated and ensure regular data back-up.

The eCRF will be signed by the Principal Investigator listed on the Food and Drug Administration (FDA) 1572 form. It is the responsibility of the Principal Investigator to ensure the eCRFs are completed and submitted to Mycovia Pharmaceuticals (or designee) in an accurate and timely manner. The processing of eCRFs will include an audit trail (to include changes made, reason for change, date of change, and person making change). At the completion of the study, the Investigator will be provided with a final copy of the eCRFs for their subjects. Mycovia Pharmaceuticals will be provided with a final copy of all subject eCRF data for the study.

Management of clinical data will be performed in accordance with applicable Mycovia Pharmaceuticals standards and data cleaning procedures to ensure the integrity of the data (e.g., removing errors and inconsistencies in the data). AEs and concomitant medications will be coded using MedDRA®. Electronic CRFs (including queries and audit trails) will be retained by the Mycovia Pharmaceuticals and copies will be sent to the Investigator to maintain as the Investigator copy.

13.7 Study and Site Closure

Upon completion or premature discontinuation of the study, the representative (or designated clinical study monitor) of Mycovia Pharmaceuticals will conduct site closure activities with the Investigator or site staff, as appropriate, in accordance with applicable regulations including GCP. Mycovia Pharmaceuticals reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at 1 or more or at all sites. If the Sponsor determines such action is needed, Mycovia Pharmaceuticals will discuss the reasons for taking such action with the Investigator or head of the medical institution (where applicable). When feasible, Mycovia Pharmaceuticals will provide advance notification to the Investigator or head of the medical institution (where applicable) of the impending action. If the study is suspended or prematurely discontinued for safety reasons, Mycovia Pharmaceuticals will promptly inform all Investigators, heads of medical institutions (where applicable), and/or institutions conducting the study. Mycovia Pharmaceuticals will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action. If required by applicable regulations, the Investigator must inform the IRB/IEC promptly and provide the reason(s) for the suspension or premature discontinuation.

13.8 Records Retention

Following closure of the study, the Investigator must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location. The records must be maintained to allow easy and timely retrieval when needed (e.g., for a Mycovia Pharmaceuticals audit or regulatory inspection) and must be available for review in conjunction with the assessment of the facility, supporting systems, and relevant site staff. When permitted by local laws/regulations or institutional policy, some or all of the records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The Investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and

meet accessibility and retrieval standards, including regenerating a hard copy, if required. Furthermore, the Investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

Investigators are required to retain essential documents pertaining to the conduct of this study for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product, per ICH guidelines. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements, local laws or regulations, or Mycovia Pharmaceuticals' standards/procedures. The Investigator must notify Mycovia Pharmaceuticals of any changes to the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the Investigator is no longer associated with the site.

13.9 Disclosure of Data

The Investigator agrees by his/her participation that the results of this study may be used for submission to national and/or international registration and supervising authorities. If required, these authorities will be provided with the names of Investigators, their addresses, qualifications, and extent of involvement. It is understood that the Investigator is required to provide Mycovia Pharmaceuticals with all study data, complete reports, and access to all study records.

Data generated by this study must be available for inspection by the United States FDA and other regulatory authorities, by Mycovia Pharmaceuticals, and the IRB/IEC as appropriate. At a subject's request, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. Subject medical information obtained during this study is confidential and disclosure to third parties other than those noted above is prohibited.

13.10 Financial Disclosure

The United States FDA Financial Disclosure by Clinical Investigators (21 Code of Federal Regulations 54) regulations require Sponsors to obtain certain financial information from Investigators participating in covered clinical studies; each Principal Investigator and Sub-Investigator is required to provide the required financial information and to promptly update Mycovia Pharmaceuticals with any relevant changes to their financial information throughout the course of the clinical study and for up to 1 year after its completion. This rule

applies to all Investigators and Sub-Investigators participating in covered clinical studies to be submitted to the FDA in support of an application for market approval.

13.11 Publication Policy

The publication policy is outlined in the Clinical Trial Agreement.

13.12 Confidentiality

Confidentiality is outlined in the Clinical Trial Agreement.

13.12.1 Data

All information about the nature of the proposed investigation provided by Mycovia Pharmaceuticals or the designated clinical study monitor to the Investigator (with the exception of information required by law or regulations to be disclosed to the IRB/IEC, the subject, or the appropriate regulatory authority) must be kept in confidence by the Investigator.

13.12.2 Subject Anonymity

The anonymity of participating subjects must be maintained. Subjects will be identified by an assigned subject number on CRFs and other documents retrieved from the site or sent to the designated clinical study monitor, Sponsor, regulatory agencies, or central laboratories/reviewers. Documents that identify the subject (e.g., the signed informed consent document, subject identification record) must be maintained in strict confidence by the Investigator, except to the extent necessary to allow auditing by the appropriate regulatory authority, the clinical study monitor, or Mycovia Pharmaceuticals representatives.

14 REFERENCES

Barousse, M., et al. Vaginal yeast colonisation, prevalence of vaginitis, and associated local immunity in adolescents. Sexually Transmitted Infections, 2004;80(1):48-53.

Bates DW and Yu DT. Clinical impact of drug-drug interactions with systemic azole antifungals. Drugs Today 2003; 39: 801-813.

Blostein, F., et al. Recurrent vulvovaginal candidiasis. Annals of Epidemiology, 2017: In press.

Diflucan® 150 Capsules [Summary of Product Characteristics]. Pfizer Limited. Sandwich, UK. Accessed through http://www.medicines.org.uk/emc/medicine/1458/spc. Last updated 19-May-2017.

Eschenbach DA. Chronic Vulvovaginal Candidiasis. New Engl J Med 2004; 351: 851-852.

Fidel, P., Jr. and J. Sobel. Host defense against vaginal candidiasis. Candida and candidiasis, ed. R. Calderone. Washington, D.C.: ASM Press. 2002, 193-209.

Foxman B, Muraglia R, Dietz JP, et al. Prevelence of recurrent Vulvovaginal Candidiasis in 5 European countries and the United States: results from an internet panel survey. Am Soc of Colposcopy and Cervical Path 2013; 17(3): 340-345.

Garvey EP, Fidel PL, Lilly EA, et al. The clinical antifungal agent VT-1161 is orally efficacious in a murine model of C. albicans vaginitis. Presented at the 11th American Society for Microbiology Conference on Candida and Candidiasis, San Francisco, CA. Abstract #33C (2012).

Goncalves B, Ferreira C, Alves CT, et al. Vulvovaginal candidiasis: epidemiology, microbiology and risk factors. Crit Rev Microbiol 2016; 42(2): 905-927.

Joishy, M., et al., Do we need to treat vulvovaginitis in prepubertal girls? British Medical Journal, 2005;330(7484):186-188.

Pfizer, I. Diflucan®, fluconazole tablet, <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=f694c617-3383-416c-91b6-b94fda371204> (2017).

Sobel JD. Recurrent vulvovaginal candidiasis. Am J Obstet Gynecol. 2016 (1):6.

Sobel JD, Wiesenfeld HC, Martens M, et al. Maintenance fluconazole therapy for recurrent Vulvovaginal Candidiasis. New Engl J Med 2004; 351:876-883.

Sobel JD. Vulvovaginal Candidosis. Lancet 2007; 369:1961-1971.

VT-1161 Investigational Brochure, v005. Durham, NC. Mycovia Pharmaceuticals Inc. (2017).

Yoshida Y. Cytochrome P450 of fungi: primary target for azole antifungal agents. Curr Top Med Mycol 1988; 2: 388-418.

Zarn JA, Bruschweiler BJ, Schlatter JR. Azole fungicides affect mammalian steroidogenesis by inhibiting sterol 14α-demethylase and aromatase. Env Health Pers 2003; 111: 255-261.

APPENDICES

Appendix A. Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table (Draft November 2007) Modified for Use in VMT-VT-1161-CL-017 Study

*This toxicity table is applicable for subjects ages 12-17 years of age.

ABBREVIATIONS: Abbreviations utilized in the Table:

ULN = Upper Limit of Normal	LLN = Lower Limit of Normal
Rx = Therapy	Req = Required
Mod = Moderate	IV = Intravenous
ADL = Activities of Daily Living	Dec = Decreased

ESTIMATING SEVERITY GRADE

For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

GRADE 1 **Mild**: Transient or mild discomfort (<48 hours); no medical intervention/therapy required

GRADE 2 **Moderate**: Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required

GRADE 3 **Severe**: Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible.

GRADE 4 **Life-threatening**: Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

SERIOUS OR LIFE-THREATENING AEs

ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a Grade 4 event.

LABORATORY RANGES

Where discrepancies in the ULN and LLN of laboratory ranges occur between those included in this document and those of the laboratory that performs the assays, the values provided by the laboratory will be used for assignment of severity grade.

	Grade 1	Grade 2	Grade 3	Grade 4
HEMATOLOGY				
Hemoglobin	9.5 – 10.5 gm/dL	8.0 – 9.4 gm/dL	6.5 – 7.9 gm/dL	< 6.5 gm/dL
	5.9 – 6.5 mmol/L	5.0 – 5.8 mmol/L	4.0 – 4.9 mmol/L	< 4.0 mmol/L
Absolute Neutrophil Count	1000 – 1500/mm^3	750 – 999/mm^3	500 – 749/mm^3	<500/mm^3
Platelets	75,000 – 99,999/mm^3	50,000 – 74,999/mm^3	20,000 – 49,999/mm^3	<20,000/mm^3
WBCs	11,000 – 13,000/ mm^3	13,000 – 15,000 /mm^3	15,000 – 30,000/mm^3	>30,000 or <1,000 mm^3
% Polymorphonuclear Leukocytes + Band Cells	> 80%	90 – 95%	>95%	---------
Activated Partial Thromboplastin (APTT)	1.01 – 1.66 × ULN	1.67 – 2.33 × ULN	2.34 – 3 × ULN	> 3 × ULN
CHEMISTRIES				
Hyponatremia	130 – 135 mEq/L or mmol/L	123 – 129 mEq/L or mmol/L	116 – 122 mEq/L or mmol/L	< 116 mEq/L or mmol/L OR abnormal sodium *with* mental status changes or seizures
Hypernatremia	146 – 150 mEq/L or mmol/L	151 – 157 mEq/L or mmol/L	158 – 165 mEq/L or mmol/L	> 165 mEq/L or mmol/L OR abnormal sodium *with* mental status changes or seizures
Hypokalemia	3.0 – 3.4 mEq/L or mmol/L	2.5 – 2.9 mEq/L or mmol/L	2.0 – 2.4 mEq/L or mmol/L OR intensive replacement therapy or hospitalization required	< 2.0 mEq/L or mmol/L OR abnormal potassium *with* paresis, ileus or life-threatening arrhythmia
Hyperkalemia	5.6 – 6.0 mEq/L or mmol/L	6.1 – 6.5 mEq/L or mmol/L	6.6 – 7.0 mEq/l or mmol/L	>7.0 mEq/L or mmol/L OR abnormal potassium *with* life-threatening arrhythmia
Hypoglycemia	55 – 64 mg/dL	40 – 54 mg/dL	30 – 39 mg/dL	<30 mg/dL or abnormal glucose *with* mental status changes or coma

	Grade 1	Grade 2	Grade 3	Grade 4
	3.1 – 3.6 mmol/L	2.2 – 3.0 mmol/L	1.7 – 2.2 mmol/L	<1.7 mmol/L or abnormal glucose *with* mental status changes or coma
Hyperglycemia (non-fasting and no prior diabetes)	116 – 160 mg/dL	161– 250 mg/dL	251 – 500 mg/dL	> 500 mg/dL or abnormal glucose *with* ketoacidosis or seizures
	6.4 – 8.9 mmol/L	8.9 – 13.9 mmol/L	13.9 – 27.8 mmol/L	>27.8 mmol/L or abnormal glucose with ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 – 7.8 mg/dL	7.7 – 7.0 mg/dL	6.9 – 6.1 mg/dL	< 6.1 mg/Dl or abnormal calcium *with* life-threatening arrhythmia or tetany
	2.10 – 1.94 mmol/L	1.93 – 1.75 mmol/L	1.74 – 1.60 mmol/L	<1.60 mmol/L or abnormal calcium *with* life-threatening arrhythmia or tetany
Hypercalcemia (correct for albumin)	10.6 – 11.5 mg/dL	11.6 – 12.5 mg/dL	12.6 – 13.5 mg/dL	> 13.5 mg/dL or abnormal calcium *with* life-threatening arrhythmia
	2.64 – 2.87 mmol/L	2.88 – 3.12 mmol/L	3.13 – 3.37 mmol/L	>3.37 mmol/L or abnormal calcium *with* life-threatening arrhythmia
Hypomagnesemia	1.4 – 1.2 mEq/L	1.1 – 0.9 mEq/L	0.8 – 0.6 mEq/L	< 0.6 mEq/L or abnormal magnesium *with* life-threatening arrhythmia
	0.58 – 0.49 mmol/L	0.48 – 0.37 mmol/L	0.36 – 0.25 mmol/L	<0.25 mmol/L or abnormal magnesium *with* life-threatening arrhythmia

	Grade 1	Grade 2	Grade 3	Grade 4
Hypophosphatemia	2.0 – 2.4 mg/dL	1.5 – 1.9 mg/dL or replacement Rx required	1.0 – 1.4 mg/dL intensive therapy or hospitalization required	< 1.0 mg/dL or abnormal phosphate *with* life-threatening arrhythmia
	0.65 – 0.77 mmol/L	0.48 – 0.64 mmol/L	0.32 – 0.47 mmol/L	<0.32 mmol/L or abnormal phosphate *with* life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any *increase* in other liver function test)	1.1 – <1.25 x ULN	1.25 – <1.5 x ULN	1.5 – 1.75 x ULN	> 1.75 x ULN
Hyperbilirubinemia (when other liver function is in normal range)	1.1 – <1.5 x ULN	1.5 – <2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
BUN	1.25 – 2.5 x ULN	2.6 – 5 x ULN	5.1 – 10 x ULN	> 10 x ULN
Hyperuricemia (uric acid)	7.5 – 10.0 mg/dL	10.1 – 12.0 mg/dL	12.1 – 15.0 mg/dL	>15.0 mg/dL
	446 – 594 µmol/L	595 – 714 µmol/L	715 – 892 µmol/L	>892 µmol/L
Creatinine	1.1 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 6 x ULN	> 6 x ULN or dialysis required
ENZYMES				
AST (SGOT)	1.1 – <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
ALT (SGPT)	1.1 – <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Alkaline Phosphatase	1.1 – <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
URINALYSIS				
Proteinuria	1+ or 200 mg - 1 gm loss/day	2-3+ or 1- 2 gm loss/day	4+ or 2-3.5 gm loss/day	nephrotic syndrome or > 3.5 gm loss/day
Hematuria	microscopic only <10 rbc/hpf	gross, no clots >10 rbc/hpf	gross, with or without clots, OR red blood cell casts	obstructive or required transfusion
CARDIOVASCULAR				
Cardiac Rhythm		asymptomatic, transient signs, no Rx required	recurrent/persistent symptomatic Rx required	unstable dysrythmia; hospitalization and treatment required

	Grade 1	Grade 2	Grade 3	Grade 4
Hypertension	transient increase > 20 mm/Hg; no treatment	recurrent, chronic increase > 20mm/Hg. /treatment required	acute treatment required; outpatient treatment or hospitalization possible	end organ damage or hospitalization required
Hypotension	transient orthostatic hypotension with heart rate increased by <20 beat/min or decreased by <10 mm Hg systolic BP, no treatment required	symptoms due to orthostatic hypotension or BP decreased by <20 mm Hg systolic; correctable with oral fluid treatment	requires IV fluids; no hospitalization required	mean arterial pressure <60mm/ Hg or end organ damage or shock; requires hospitalization and vasopressor treatment
Pericarditis	minimal effusion	mild/moderate asymptomatic effusion, no treatment	symptomatic effusion; pain; ECG changes	tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	microscopic/occult	mild, no transfusion	gross blood loss; 1-2 units transfused	massive blood loss; > 3 units transfused
RESPIRATORY				
Cough	transient- no treatment	persistent cough; treatment responsive	Paroxysmal cough; uncontrolled with treatment	----------
Bronchospasm, Acute	transient; no treatment; 70% – 80% FEV_1 of peak flow	requires treatment; normalizes with bronchodilator; FEV_1 50% – 70% (of peak flow)	no normalization with bronchodilator; FEV_1 25% – 50% of peak flow; or retractions present	cyanosis: FEV_1 < 25% of peak flow or intubation necessary
Dyspnea	dyspnea on exertion	dyspnea with normal activity	Dyspnea at rest	Dyspnea requiring oxygen therapy
GASTROINTESTINAL				
Nausea	mild or transient; maintains reasonable intake	moderate discomfort; intake decreased significantly; some activity limited	no significant intake; requires IV fluids	hospitalization required;
Vomiting	1 episode in 24 hours	2-5 episodes in 24 hours	>6 episodes in 24 hours or needing IV fluids	physiologic consequences requiring hospitalization or requiring parenteral nutrition

	Grade 1	Grade 2	Grade 3	Grade 4
Constipation	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Diarrhea	mild or transient; 3-4 loose stools/day or mild diarrhea last < 1 week	moderate or persistent; 5-7 loose stools/day or diarrhea lasting >1 week	>7 loose stools/day or bloody diarrhea; or orthostatic hypotension or electrolyte imbalance or >2L IV fluids required	hypotensive shock or physiologic consequences requiring hospitalization
Oral Discomfort/Dysphagia	mild discomfort; no difficulty swallowing	some limits on eating/drinking	eating/talking very limited; unable to swallow solid foods	unable to drink fluids; requires IV fluids
NEUROLOGICAL				
Neuro-Cerebellar	slight incoordination dysdiadochokinesis	intention tremor, dysmetria, slurred speech; nystagmus	locomotor ataxia	incapacitated
Psychiatric	mild anxiety or depression	moderate anxiety or depression; therapy required; change in normal routine	severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation	acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations
Muscle Strength	subjective weakness, no objective symptoms/ signs	mild objective signs/symptoms no decrease in function	objective weakness function limited	paralysis
Paresthesia (burning, tingling, etc.)	mild discomfort; no treatment required	moderate discomfort; non-narcotic analgesia required	severe discomfort; or narcotic analgesia required with symptomatic improvement	incapacitating; or not responsive to narcotic analgesia
Neuro-sensory	mild impairment in sensation (decreased sensation, e.g., vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution; or change in taste, smell, vision and/or hearing	moderate impairment (mod decreased sensation, e.g., vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical	severe impairment (decreased or loss of sensation to knees or wrists) or loss of sensation of at least mod degree in multiple different body areas (i.e., upper and lower extremities)	sensory loss involves limbs and trunk; paralysis; or seizures

	Grade 1	Grade 2	Grade 3	Grade 4
MUSCULOSKELETAL				
Arthralgia (joint pain)	mild pain not interfering with function	moderate pain, analgesics and/or pain interfering with function but not with activities of daily living	severe pain; pain and/or analgesics interfering with activities of daily living	disabling pain
Arthritis	mild pain with inflammation, erythema or joint swelling – but not interfering with function	moderate pain with inflammation, erythema or joint swelling – interfering with function, but not with activities of daily living	severe pain with inflammation, erythema or joint swelling –and interfering with activities of daily living	permanent and/or disabling joint destruction
Myalgia	Myalgia with no limitation of activity	muscle tenderness (at other than injection site) or with moderate impairment of activity	severe muscle tenderness with marked impairment of activity	frank myonecrosis
SKIN				
Mucocutaneous	erythema; pruritus	diffuse, maculo papular rash, dry desquamation	vesiculation or moist desquamation or ulceration	exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery
Induration	< 15mm	15 – 30 mm	>30mm	
Erythema	< 15mm	15 – 30 mm	>30mm	
Edema	< 15mm	15 – 30 mm	>30mm	
Rash at Injection Site	< 15mm	15 – 30 mm	>30mm	
Pruritus	slight itching at injection site	moderate itching at injection extremity	itching over entire body	
SYSTEMIC				
Allergic Reaction	pruritus without rash	localized urticaria	generalized urticaria; angioedema	anaphylaxis
Headache	mild, no treatment required	transient, moderate; treatment required	severe; responds to initial narcotic therapy	intractable; requires repeated narcotic therapy

	Grade 1	Grade 2	Grade 3	Grade 4
Fever: oral	37.7 – 38.5° C or 100.0 – 101.5 °F	38.6 – 39.5 °C or 101.6 – 102.9 °F	39.6 – 40.5 °C or 103 – 105 °F	> 40 °C or > 105 °F
Fatigue	normal activity reduced < 48 hours	normal activity decreased 25- 50% > 48 hours	normal activity decreased > 50% cannot work	unable to care for self

Appendix B: Grading of Renal Impairment

Category	GFR categories in CKD GFR ml/min/1.73 m^2	Terms
G1	≥90	Normal or high
G2	60 – 89	Mildly decreased*
G3a	45 – 59	Mildly to moderately decreased
G3b	**30 – 44**	**Moderately to severely decreased**
G4	**15 – 29**	**Severely decreased**
G5	**<15**	**Kidney failure**

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.
*Relative to young adult level.
In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.

Albuminuria categories in CKD		
Category	**ACR (mg/g)**	**Terms**
A1	<30	Normal to mildly increased
A2	**30 – 300**	**Moderately increased***
A3	**>300**	**Severely increased****

Abbreviations: ACR, albumin-to-creatinine ratio; CKD, chronic kidney disease.
*Relative to young adult level.
**Including nephrotic syndrome (albumin excretion ACR >2220 mg/g)

Reference: https://www.kidney.org/professionals/explore-your-knowledge/how-to-classify-ckd

Appendix C: Child-Pugh Classification of Hepatic Impairment

The Child- Pugh classification is a means of assessing the severity of liver cirrhosis.

Score	1	2	3
bilirubin (micromol/l)	<34	34 – 50	>50
albumin (g/l)	>35	28 – 35	<28
PT (s prolonged)	<4	4 – 6	>6
encephalopathy	none	mild	marked
ascites	none	mild	marked

If there is primary biliary cirrhosis or sclerosing cholangitis then bilirubin is classified as <68 =1; 6 – 170 = 2; >170 = 3.

The individual scores are summed and then grouped as:

- <7 = A (Mild impairment)
- 7 – 9 = B (Moderate impairment)
- >9 = C (Severe impairment)

A C classification forecasts a survival of less than 12 months.

From: Pugh RNH, Murray-Lyon IM, Dawson JL et al. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60:649-9.

Appendix D. Protocol Amendment 1, Version 2 Summary of Protocol Changes

Section	Change	Reason	Impact on Human Subject (risk/benefit)
Synopsis	Added '.. except for HIV, HBsAg and antibodies to hepatitis C virus' and 'e. Positive test for antibodies to human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or antibodies to hepatitis C virus.' to Excl. # 16.	Inadvertently left out of the synopsis.	N/A
Synopsis	Added '**Maintenance Treatment Phase'**	Added header	N/A
Synopsis	Changed 'patients' to 'subjects'.	Corrected error	N/A
Synopsis, Sect. 7.4.1 #3	Added 'urogenital'.	Add clarification on type of concomitant infections.	Benefit
Synopsis, Sect. 5.1	Added 'results' to Incl. #5.	Provide clarification that the results must be present at the Screening visit.	Benefit
Synopsis, Sect. 5.1	Added 'used continuously and successfully for at least 90 days prior to first dose of study drug' to Incl #10 Option 1, #1.	Provide guidance on length of time of use of contraceptive method	Benefit
Synopsis, Sect. 5.1	Added 'used successfully for at least 90 days prior to first dose of study drug' to Incl #10 Option 1, #2 and #3 and Option 2, #1 and #2.	Provide guidance on length of time of use of contraceptive method	Benefit
Synopsis, Sect. 5.1	Added '(vasectomy performed at least 6 months prior to first dose of study drug)' to Incl #10 Option 1, #4.	Provide guidance on contraception methods women with vasectomized male partners	Benefit
Synopsis, Sect. 5.1	Added language and move to subscript **a**, 'Subjects who started using an intrauterine device or any of the hormonal contraceptive methods described above less than 3 months prior to the first dose of study medication must agree to use a double-barrier method (i.e., diaphragm plus spermicide or condom) through 3 months after start of the use of the IUD or hormonal	Provide clarification on the birth control	Benefit

	contraceptive. Similarly, subjects that claim a monogamous relationship with a vasectomized male partner where the vasectomy was performed less than 6 months prior to the first dose of study medication, must agree to use a double-barrier method (i.e., diaphragm plus spermicide or condom) through 6 months after the date of the vasectomy.'		
Synopsis, Sect. 5.2	Added '; nor use of topical vulvar or vaginal steroids during the study or within 7 days prior to Screening visit' to Excl. #5.	Clarification on prohibited use of vulvar and vaginal steroids and the wash out period.	Benefit
Synopsis, Sect. 5.2	Added 'collunarium/nasal' to Excl. #5.	Additional method permitted.	Benefit
Synopsis, Sect. 5.2	Added 'for the treatment of bacterial vaginosis, trichomonas, or other concomitant urogenital infection' to Excl. #6.	Provide specification on type of treatment.	Benefit
Synopsis	Corrected from 12.5 to 15% non-inferiority margin.	Error correction	N/A
Synopsis, Sect. 10.1	Added 'with ±10-minute window per timepoint'.	Provide a time window for intense PK timepoints.	N/A
Table 1	Changed in footnote g '12' to '14' and '24' to '26'.	Error correction	N/A
Table 1	Removed 'X' in the table for Administer VT-1161 or Placebo at Weeks 8 and 14	Error correction	N/A
Sect. 1.3	Added '…approved…often', changed 'better' to 'improved', changed 'it' to 'VT-1161', changed 'Its' to 'The', and added 'asociated with VT-1161'.	Provided improved text in section.	N/A
Sect. 7.1.2	Added 'returning to the site approximately 14 days after the first dose of VT-1161 or over-encapsulated fluconazole and demonstrating resolution of the VVC infection (defined by a signs and symptoms score of <3)….. if initially randomized to receive VT-1161….. if initially randomized to receive fluconazole'.	Provide additional information for qualifying subjects entering the Maintenance Phase.	Benefit

Sect. 8.1.1	Added 'Safety'.	Provided clarification on type of laboratory results.	N/A
Sect. 8.1.2	Added '(±2 Days)'	Provide visit window for Day 14	Benefit
Sect. 8.1.3	Removed 'Obtain serum sample for pregnancy testing for all WOCBP.'	Corrected error.	N/A
Sect. 8.1.3	Add 'Subjects with clinical signs and symptoms score of < 3 will continue into Maintenance Phase and subjects with score of ≥3 will be an Induction failure, ending study participation.'	Provided criteria for subjects to enter Maintenance Phase.	Benefit
Sect. 11.2	Added 'The incidence or severity of AEs in the study indicates a potential health hazard to subjects' and 'A subject may be withdrawn due to lack of tolerability or safety concerns, including study drug-related AEs or development of clinically-significant study drug-related laboratory abnormalities. If a subject is withdrawn from treatment, the subject must be followed clinically until the event is resolved or deemed stable. A subject must be discontinued from the study drug if ALT or/and AST is > 5 ×times the upper limit of normal (ULN) or ALT or/and AST is > 3 ×times the ULN and serum total bilirubin is > 2.0 times the ULN', and 'Subjects who prematurely discontinue study medication, but remain in the study, may be treated according to the standard local practice.' Replaced 'do so' with 'remain in the study'.	Provide further clarification on subject withdrawals and discontinuation.	Benefit
Sect 11.3	Added 'Study completion is defined as when the last subject has completed their last study visit.'	Provided definition for study completion.	N/A