

Clinicaltrials.gov ID: NCT02308046

NCT02308033

NCT02308007

Protocol ID: MTC-001 (Trials 1, 2 and 3)

Brief Title: Multi-Center Study of New Medications to Treat Vaginal Infections (SMART GIVES)

Official Title: Solubilized Metronidazole And/oR Terconazole Gels Intra-Vaginal Efficacy and Safety (SMART GIVES)

Document Type: Protocol

Date of Document: March 12, 2015

Sponsor: Curatek Pharmaceuticals, LLC

Protocol Number: MTC-001

IND # 121,229
124,679
124,680

**Solubilized Metronidazole And/oR Terconazole Gels Intra-Vaginal Efficacy
and Safety
(SMART GIVES)**

Phase III

Original Protocol
Version 1.0 12/12/14

Revised Protocol
Version 2.0 03/12/15

Curatek Pharmaceuticals, LLC
1965 Pratt Boulevard
Elk Grove Village, IL 60007

CONFIDENTIAL

This confidential document is the property of Curatek Pharmaceuticals, LLC. No unpublished information contained herein may be disclosed without prior written approval from Curatek Pharmaceuticals, LLC. Access to this document must be restricted to relevant parties.

1. Signatures

1.1. Protocol Approval Form
Solubilized Metronidazole And/oR Terconazole Gels Intra-Vaginal Efficacy and Safety
(SMART GIVES)

Internal Personnel

[Redacted Signature]

3/27/15
Date

External Personnel

[Redacted Signature]

3/31/15
Date

Protocol Number: MTC-001

IND # 121,229

124,679

124,680

1.2. Investigator Agreement

Protocol Title: Solubilized Metronidazole And/oR Terconazole Gels Intra-Vaginal Efficacy and Safety (SMART GIVES)

I have read the above named protocol, and agree to personally conduct or supervise the trial as described. I verify that I am qualified by education, training, and experience to conduct the trial and will do so in accordance with all applicable regulatory requirements, and in accordance with Good Clinical Practice (GCP).

I will provide copies of the protocol and all relevant study materials to study personnel who will have delegated responsibilities for this study and I will ensure they are all adequately trained regarding the protocol, investigational products (IPs)/study drugs, the conduct of the study, and their associated responsibilities.

I agree that no subjects will be enrolled in the trial until the protocol and informed consent have been Institutional Review Board (IRB) approved. All subjects will be properly consented prior to any study procedures being performed.

I have read the Investigator’s Brochure and agree to report all adverse events that occur during the trial.

My records (written and/or electronic), subject reports, and all relevant source documentation will be used to transcribe information onto each subject’s case report form (CRF). By signing the CRF, I will attest to the authenticity of the data and the accuracy and completeness of the transcriptions. I agree to the auditing and monitoring procedures described in the protocol and will provide full and unencumbered access to source documents and medical records to auditors, monitors, the reviewing IRB, Curatek representatives, and government regulatory agencies (i.e. Food and Drug Administration [FDA]), as applicable.

I will provide Curatek/Curatek’s designee (Clinical Research Organization [CRO]) with all data generated during the trial and I understand that all information concerning the investigational products/study drugs are confidential and the exclusive property of Curatek. I will abide by all terms outlined in the Clinical Trial Agreement (CTA).

Investigator Signature: _____ Date: _____

Investigator Name (print): _____

Name and Address of Clinical Site: _____

2. Protocol Synopsis

Sponsor	Curatek Pharmaceuticals, LLC
Protocol Number	MTC-001
Protocol Title	Solubilized Metronidazole And/oR Terconazole Gels Intra-Vaginal Efficacy and Safety (SMART GIVES)
Study Design and Objectives	<p>This will be a multi-center, phase III trial, comprised of three studies, each designed to test the safety and efficacy of a different investigational product, for a specific vaginal infection/indication. They are:</p> <ol style="list-style-type: none"> 1. Bacterial Vaginosis (BV) Study: A randomized, double-blind, parallel-group, placebo-controlled study to test the safety and efficacy of BV Gel (0.9% metronidazole gel) for the treatment of BV 2. Vulvovaginal Candidiasis (VVC) Study: A randomized, double-blind, parallel-group, placebo-controlled study to test the safety and efficacy of VVC Gel (0.8% terconazole gel) for the treatment of VVC 3. Mixed Infection (Concurrent BV and VVC) Study: A randomized, double-blind, parallel-group, active-controlled study to test the safety and efficacy of Combo Gel (0.9% metronidazole gel and 0.8% terconazole gel) for the treatment of Mixed Infection <p>Subjects who sign an informed consent form (ICF), are diagnosed with BV, VVC, or Mixed Infection, and meet all other eligibility requirements as specified in the inclusion/exclusion criteria will be enrolled into one of the three vaginal infection studies listed above and subsequently randomized to treatment based on clinical diagnosis at the screening and enrollment/baseline visit (Visit 1). BV subjects will be entered into the BV Study, VVC subjects will be entered into the VVC Study, and concurrent BV and VVC (Mixed Infection) subjects will be entered into the Mixed Infection Study.</p> <p>All subjects will be asked to return for a test of cure (TOC) visit (Visit 2) 7-14 days after randomization. Subjects who in the opinion of the investigator/clinician do not require additional treatment for vaginal discomfort/symptoms, and subjects who did not self-medicate for vaginal discomfort/symptoms, will be asked to return for a follow-up visit (Visit 3) 21-30 days after randomization to assess continued clinical response to treatment and adverse events.</p> <p>Study procedures will be identical in all three infection studies with the exception of safety labs (i.e. CBC with differential and chemistries) which will only be obtained at Visit 1 and Visit 2 on subjects entered into the Mixed Infection Study. There will be one case report form for each subject. The case report form will be the same for all three infection studies. Analysis of safety and efficacy will be done separately for each investigational product.</p>
Number of Study Subjects & Study Sites	Approximately 116 evaluable BV subjects, 100 evaluable VVC subjects, and 189 evaluable Mixed Infection subjects will be required. [REDACTED]

	<p>The study will be conducted at approximately 40 centers in the United States.</p> <p>Enrollment is expected to last approximately [redacted] months.</p>
<p>Duration of Treatment and Study Duration</p>	<p>The duration of treatment is three days and the duration of participation for each subject is approximately 30 days from randomization.</p>
<p>Inclusion Criteria</p>	<ul style="list-style-type: none"> • Clinical diagnosis of BV based on the presence of ALL of the following: <ul style="list-style-type: none"> ○ Amsel criteria (<u>all four</u> of the following criteria must be present): <ol style="list-style-type: none"> 1. Abnormal vaginal discharge consistent with BV (i.e. off-white [milky or gray], thin, homogeneous discharge)^a 2. Vaginal secretion pH of > 4.5 3. A fishy odor of the vaginal discharge with the addition of a drop of 10% potassium hydroxide (KOH) (i.e. a positive “whiff test”) 4. Presence of clue cells \geq 20% of the total epithelial cells on microscopic examination of the saline wet mount <p style="text-align: center;">AND</p> ○ Nugent score \geq 4 based on Gram stain slide <p style="text-align: center;">AND/OR</p> • Clinical diagnosis of VVC based on the presence of ALL of the following: <ul style="list-style-type: none"> ○ A composite signs and symptoms score \geq 2 based on rating the following six vaginal/vulvar signs and symptoms on a severity scale where absent =0, mild =1, moderate =2 and severe =3: <ol style="list-style-type: none"> 1. Itching 2. Burning 3. Irritation 4. Edema 5. Erythema 6. Excoriation ○ Presence of yeast forms (hyphae/pseudohyphae) or budding yeasts seen on microscopic examination of a KOH prepared slide of vaginal secretions <p style="text-align: center;">AND</p> • Mycologic diagnosis of VVC based on positive culture for <i>Candida</i> species <p style="text-align: center;">AND</p> <ul style="list-style-type: none"> • At least 12 years of age • Capable of providing written informed consent; if a minor, capable of assent

^a Subjects with Mixed Infection (i.e. concurrent BV and VVC) may have an abnormal discharge consistent with BV, consistent with VVC (i.e. white, creamy, and curdy [cottage cheese like] adherent to the epithelium), or an abnormal discharge of varying characteristics with relation to odor, color, and consistency.

	<p>with parent/legal guardian available to provide written informed consent</p> <ul style="list-style-type: none"> • Willing to begin treatment within 2 days of the baseline visit (Visit 1) • Currently not menstruating and not anticipating menses during treatment • Willing to abstain from sexual intercourse through Visit 2 and have their partner use a non-lubricated condom within the preceding 48 hours of Visit 3 if sexual intercourse occurs • Willing to abstain from using intravaginal/vulvovaginal products (e.g. feminine hygiene products such as douches and deodorants; contraceptive products such as diaphragms, spermicidal creams, gels, and foams; vaginal lubricants, moisturizers, and hormonal suppositories and creams such as Vagifem®, Estrace® and Premarin® cream; and tampons etc.) through Visit 2 and within 48 hours of Visit 3. • Willing to abstain from alcohol and propylene glycol ingestion during treatment and for 1 day thereafter • If heterosexually active, subject must be post-menopausal for ≥ 1 year, surgically sterile (i.e. hysterectomy, bilateral oophorectomy, or bilateral tubal ligation), sexually active with a male partner who is surgically sterile (i.e. vasectomy), or practicing an acceptable form of birth control (i.e. oral contraceptives, contraceptive injections, contraceptive patch, condoms, or intrauterine device [IUD]) for at least 1 month before study entry and agree to continue the contraceptive method for the duration of the study. If sexually abstinent, subjects must agree to continue abstinence or use an acceptable method of birth control should sexual activity commence during the study. • Willing and capable of cooperating to the extent and degree required by the protocol • Negative urine pregnancy test (unless subject is surgically sterile or post-menopausal ≥ 1 year)
<p>Exclusion Criteria</p>	<p><i>Exclusion Criteria Applicable to all Infection Studies</i></p> <ul style="list-style-type: none"> • Other infectious causes of vulvovaginitis (e.g. <i>Trichomonas vaginalis</i>, <i>Chlamydia trachomatis</i>, <i>Neisseria gonorrhoeae</i>, active <i>Herpes simplex</i> virus or genital warts) • Subject has used systemic (oral, intravenous [IV], or intramuscular [IM]), intravaginal/vulvovaginal antifungal, antimicrobial, or corticosteroid therapy within 14 days of study enrollment • Subject is currently taking or has taken disulfiram therapy within 14 days of study enrollment • Subject is currently on lithium, coumarin anticoagulants (e.g. warfarin), or immunosuppressive therapy • Subject is expected to require the concomitant use of prohibited medications/products while enrolled in the study • Subject will require treatment for cervical intra-epithelial neoplasia (CIN) or cervical carcinoma while enrolled in the study or plans to use other investigational products while enrolled in the study • Nursing mother • Use of any investigational drug within 30 days of enrollment or plans to use other investigational products while enrolled in the study

	<ul style="list-style-type: none"> • Known primary or secondary immunodeficiency • Presence of any condition or illness, including vulvar and vaginal conditions, that in the opinion of the investigator would preclude accurate evaluation of the subject's condition and/or confound the interpretation of the subject's treatment response • History of hypersensitivity to metronidazole or other nitroimidazoles; terconazole or other triazoles; parabens; or any other ingredient/component of the formulations <p>Subjects who meet criteria for BV only will be entered into the BV Study and randomized to a BV treatment (BV Gel or Placebo Gel), subjects who meet criteria for VVC only will be entered into the VVC Study and randomized to a VVC treatment (VVC Gel or Placebo Gel) and subjects who meet criteria for both BV and VVC will be entered into the Mixed Infection Study and randomized to treatment (BV Gel, VVC Gel, or Combo Gel) for Mixed Infection.</p>
<p>Study Procedures</p>	<p><u>Screening and Enrollment/Baseline Visit (Visit 1)</u></p> <p>All subjects will sign an informed consent form (ICF) and inclusion/exclusion criteria will be evaluated to determine subject eligibility. Evaluation of subject eligibility will include: demographic information; contraceptive and obstetric status, medical, surgical, and gynecologic history; symptom and sign severity rating; a physical exam with vital signs; a pelvic exam to visually inspect for genital herpes and warts, assess Amsel criteria (i.e. vaginal discharge assessment, pH assessment, whiff test, and saline wet prep), and check for the presence or absence of motile trichomonads on saline wet prep and yeast on KOH wet mount; tests for <i>Neisseria gonorrhoea</i>, <i>Chlamydia trachomatis</i>, <i>Trichomonas vaginalis</i>, and <i>Herpes simplex</i> (if suspected); culture for <i>Candida</i> species; a Gram stain; a pregnancy test (if indicated); a Pap smear if the subject is ≥ 21 years old and one was not done within the past 3 years; and hematology and chemistry labs for subjects enrolled in the Mixed Infection Study.</p> <p>Since some of the required tests for eligibility will not be immediately available at the baseline evaluation, enrollment into an infection study will be based on clinical criteria (i.e. Amsel criteria and/or signs and symptoms of VVC including KOH microscopy).</p> <p>Subjects will be randomized at Visit 1 based on infection diagnosis. They will be dispensed study drug and applicators along with instructions for the administration of the drug; a listing of study instructions; condoms; packaging for return of unused drug; and a subject diary. Subjects will record diary data between Visits 1-2.</p> <p>Subjects will be asked to return their completed diaries and their unused drug, as directed, at their next visit (Visit 2).</p> <p><u>Test of Cure Evaluation (Visit 2):</u></p> <p>Visit 2 will occur 7-14 days after randomization. If a subject is menstruating on the day of this scheduled visit, she should be rescheduled to return 24 hours after completion of menses.</p>

	<p>Visit 2 procedures will include: symptom and sign severity rating; a pelvic exam to assess Amsel criteria and to check for the presence or absence of motile trichomonads on saline wet prep; a culture for <i>Candida</i> species; a Gram stain; hematology and chemistry labs for subjects enrolled in the Mixed Infection Study; and collection of unused drug.</p> <p>Assessment of subject compliance (i.e. with study instructions and drug administration) and information on time to resolution/reoccurrence of symptoms, concomitant medication use, and possible adverse events will be obtained by interviewing the subject and reviewing the subject's diary.</p> <p>The investigator/clinician will be asked to document whether the subject requires any additional treatment for vaginal discomfort/symptoms. Subjects who do require additional treatment should be treated per investigator/clinician judgment and be terminated from the study. If a subject self-medicated for vaginal discomfort/symptoms, she should be terminated from the study.^b</p> <p>Subjects who do not require additional treatment and subjects who did not self-medicate will be asked to return for a follow-up visit (Visit 3) 21-30 days after randomization.</p> <p>For those subjects continuing in the study, subject study instructions will be reviewed. If unused study drug and/or the subject diary were not returned, the subject should be reminded to return them at the next visit.</p> <p>If at any time during the study the subject or investigator has concerns about persistent symptoms or adverse event(s), the subject may return to the office/clinic any time between visits to be evaluated (i.e. an unscheduled visit). If the subject requires treatment for vaginal discomfort/symptoms at an unscheduled visit she should be terminated from the study. If treatment is not required she may return for her next scheduled visit.</p> <p>Some Visit 1 laboratory test results used to determine whether inclusion/exclusion criteria have been met will not be available before subjects are randomized, but will become available during the course of the study. Visit 1 test results that would make a subject not eligible for the study are: positive gonorrhea, chlamydia, trichomonas, or herpes tests; normal Nugent score < 4 (for BV and Mixed Infection subjects); or negative <i>Candida</i> culture (for VVC and Mixed Infection subjects). When test results that make a subject ineligible become known, subjects should be contacted and asked to return to the office/clinic to be terminated from the study. Termination procedures for these subjects are more limited and include a safety assessment consisting of reviewing concomitant medication use, occurrence of adverse events, and obtaining hematology and chemistry labs if the subject was in the Mixed Infection Study and labs were not already obtained at Visit 2. Subject</p>
--	--

^b Self-administration of therapy includes prescription and over the counter (OTC) antimicrobial, anti-fungal, analgesics, or steroid treatments.

	<p>diaries should be reviewed, unused drug collected, and study drug administration/compliance ascertained if not already done.</p> <p><u>Follow-Up Evaluation (Visit 3):</u> Visit 3 will occur 21-30 days after randomization.</p> <p>Visit 3 procedures will include: symptom and sign severity rating; a pelvic exam to assess Amsel criteria and to check for the presence or absence of motile trichomonads on saline wet prep; a culture for <i>Candida</i> species; and a Gram stain. If any clinically significant hematology and/or chemistry lab changes were noted in Mixed Infection subjects at Visit 2, these labs may be repeated. If labs for a Mixed Infection subject were not obtained at Visit 2, they may be obtained at Visit 3. An assessment of subject compliance with study instructions, concomitant medication use, and possible adverse events will be obtained by interviewing the subject. Information on study drug administration/compliance and time to resolution/reoccurrence of symptoms, (if not previously ascertained or if updated information is available) will also be obtained by interviewing the subject.</p> <p>The investigator/clinician will be asked to document whether the subject requires any additional treatment for vaginal infection (i.e. BV, VVC, or Mixed Infection). Subjects who do require additional treatment should be treated per investigator/clinician judgment.</p> <p>Subjects will be asked to complete a subject satisfaction survey and will be terminated from the study following Visit 3.</p> <p>See Appendix A, Schedule of Procedures.</p>
<p>Efficacy Endpoints and Safety Assessments</p>	<p><u>Primary Efficacy Endpoints and End Evaluations</u></p> <ol style="list-style-type: none"> 1. BV Study: BV cure rate, with cure defined as normal/physiologic discharge^c, negative whiff test, and < 20% clue cells (i.e. clinical cure) 2. VVC Study: VVC cure rate, with cure defined as resolution of all signs and symptoms attributable to VVC (i.e. clinical cure). 3. Mixed Infection Study: Mixed Infection cure rate, with cure defined as BV cure (i.e. BV clinical cure) AND a VVC cure (i.e. VVC clinical cure) <p>Primary efficacy endpoint evaluations will occur at the subject's test-of-cure visit (Visit 2). If a subject requires additional treatment (i.e. a BV subject requiring treatment for BV, a VVC subject requiring treatment for VVC or a Mixed Infection subject requiring treatment for BV and/or VVC) or self-medicates^d for vaginal discomfort/symptoms prior to or at Visit 2 the subject will be considered a treatment failure.</p>

^c In the event a BV subject has discharge consistent with VVC (i.e. white, creamy, and curdy [cottage cheese like] adherent to the epithelium), the subject will be considered a BV cure providing all other criteria for BV cure (and evaluability) are met and the subject has a positive yeast culture.

^d Self-administration of therapy includes prescription and over the counter (OTC) antimicrobial, anti-fungal, analgesics, or steroid treatments.

	<p><u>Secondary Endpoints and Evaluations</u></p> <ol style="list-style-type: none"> 1. BV Study: BV clinical and Nugent score cure rates alone and combined; changes/improvements in Amsel criteria and Nugent scores; time to resolution of vaginal symptoms 2. VVC Study: VVC clinical (i.e. resolution of all signs and symptoms attributable to VVC) and mycologic cure rates (i.e. negative <i>Candida</i> on culture) alone and combined; changes/improvements in signs and symptoms scores; eradication (or persistence) of individual fungal species; time to resolution of vaginal symptoms 3. Mixed Infection Study: BV clinical and Nugent score cure rates alone and combined; changes/improvements in Amsel criteria and Nugent scores; VVC clinical and mycologic cure rates alone and combined; changes/improvements in signs and symptoms scores; eradication or persistence of individual fungal species; time to resolution of vaginal symptoms <p>Secondary endpoint evaluations will occur at Visits 2 and 3 and will utilize criteria appropriate to the subject's entry diagnosis (i.e. study subject was enrolled in).</p> <p><u>Safety</u></p> <p>Safety will be assessed by questioning subjects regarding any adverse events that may have occurred, concomitant medication use, review of subject diaries, and obtaining blood laboratory tests for Mixed Infection subjects.</p> <p>Safety will be assessed through summaries of adverse events (AEs) and laboratory evaluations. All safety analyses will be based on the safety population and will be summarized for each treatment group. These summaries will be presented separately for each infection study. Adverse events, as available, for BV Gel and VVC Gel will also be summarized by combining subjects who received the same treatment regimen across the studies. For example, those receiving BV Gel in the BV study will be combined with those receiving BV Gel in the Mixed Infection study.</p>
Randomization and Treatment	<p>An interactive voice response (IVR) system/interactive web response (IWR) system will randomize subjects to treatment at Visit 1 based on the infection study they are enrolled in. All treatments will consist of three doses, administered by vaginal applicator, at bedtime for three consecutive days. Subjects will be randomized to treatment as follows:</p> <ul style="list-style-type: none"> • Subjects enrolled in the BV study will receive either BV Gel (0.9% metronidazole gel) or Placebo Gel in a 1:1 ratio • Subjects enrolled in the VVC study will receive either VVC Gel (0.8% terconazole gel) or Placebo Gel in a 1:1 ratio • Subjects enrolled in the Mixed Infection study will receive either Combo Gel (0.9% metronidazole gel and 0.8% terconazole gel), or BV Gel (0.9% metronidazole gel) or VVC Gel (0.8% terconazole gel) in a 1:1:1 ratio
Dosage of Study Drug/Treatment Regimens	<ul style="list-style-type: none"> • BV Gel: 0.9% metronidazole gel (45 mg of metronidazole/5 grams of gel); total metronidazole dose = 135 mg • VVC Gel: 0.8 % terconazole gel (40 mg terconazole/5 grams of gel); total terconazole dose = 120 mg • Combination BV & VVC Gel (Combo Gel): 0.9% metronidazole gel and 0.8%

	<p>terconazole gel; total metronidazole dose = 135 mg and total terconazole dose = 120 mg</p> <ul style="list-style-type: none"> • Placebo Gel: no active ingredients
Statistical Methods	<p>Each of the three infection studies within the trial will be analyzed separately. The primary assessments of efficacy will be based on the modified intent-to-treat (mITT) population. This population will include all subjects randomized to treatment and administered at least one dose of study drug. In addition, subjects in the VVC and Mixed Infection studies must have a positive baseline vaginal fungal culture for <i>Candida</i> species. Subjects in the BV and Mixed Infection studies must have a Gram stain Nugent score of ≥ 4 at the baseline visit.</p> <p>In addition to the mITT analyses of the data, analyses will be conducted using the intent-to-treat (ITT) population (all subjects randomized to treatment) as well as the per protocol (PP) population (subset of mITT subjects that had no major protocol violations and who are classified as efficacy evaluable with no missing data required to determine primary endpoints).</p> <p>Subjects will be categorized as cure or failure for the mITT and ITT analyses and as cure, failure, or non-evaluable for the PP analysis. The number and percentage of subjects in each treatment group in each of these categories will be reported.</p> <p>BV Study and VVC Study: The primary statistical objective is to demonstrate superiority of active treatment to placebo. This will be performed by conducting a continuity corrected Chi-squared test for a difference in the proportion of cure between active and placebo. Also, a 95% two-sided confidence interval for the difference in proportion of cure between the two treatments will be constructed.</p> <p>Mixed Infection Study: The primary statistical objective of the Mixed Infection study is to demonstrate the superiority of the Combo Gel to both BV Gel and VVC Gel. The assessment of superiority will be performed by conducting continuity corrected Chi-squared tests for a difference in the proportion of Mixed Infection cure between the Combo Gel and each of the two single entity treatments. If the P-values for both of the hypothesis tests are less than or equal to 0.05, the Combo Gel will be considered superior to both of the single entity gels. Despite there being two comparisons made within the same study, no adjustment for multiplicity is necessary since both comparisons must be positive instead of “at least one,” in order to conclude superiority of the Combo Gel. Also, 95% two-sided confidence intervals for the difference in proportion of Mixed Infection cure between the Combo Gel and each of the two single entity treatments will be constructed.</p>
Sample Size	<p>Sample sizes were calculated for each infection study based on estimated cure rates for at least 90% power and 50 subjects per treatment group. Superiority tests will be performed as two-sided, $\alpha = 0.05$ level significance tests, and sample sizes were calculated using Fisher’s Exact test in case the planned Chi-squared test is not appropriate.</p> <p>BV Study: 116 per protocol, evaluable subjects VVC Study: 100 per protocol, evaluable subjects</p>

	<p>Mixed Infection Study: 189 per protocol, evaluable subjects</p> <p>When the pre-determined number of subjects is enrolled in one of the infection studies of the protocol, that study will be closed to enrollment and the remaining studies will continue to recruit/enroll subjects.</p> 
--	--

Table of Contents

1. Signatures	2
1.1. Protocol Approval Form.....	2
1.2. Investigator Agreement.....	3
2. Protocol Synopsis	4
3. Background and Rationale	16
3.1. Bacterial Vaginosis.....	16
3.2. Vulvovaginal Candidiasis	17
3.3. Rationale for Metronidazole 0.9% Vaginal Gel (BV Gel)	17
3.4. Rationale for Terconazole 0.8% Vaginal Gel (VVC Gel)	18
3.5. Rationale for Combination Metronidazole 0.9% Gel and Terconazole 0.8% Vaginal Gel (Combo Gel).....	18
3.6. Rationale for Comparators in Each Infection Study.....	18
4. Study Design	19
5. Study Objectives and Endpoints.....	20
5.1. Primary Objectives.....	20
5.2. Primary Efficacy Endpoints and Evaluations.....	21
5.3. Secondary Endpoints and Evaluations	21
6. Selection of Study Population	21
6.1. Recruitment Procedures	21
6.2. Registration Procedures.....	22
6.2.1. Screen Failures	22
6.2.2. Subject Identification Log.....	22
6.3. Inclusion/Exclusion Criteria.....	22
6.3.1. Inclusion Criteria	22
6.3.2. Exclusion Criteria Applicable to all Infection Studies.....	24
7. Study Drug.....	24
7.1. Drug Supplies.....	24
7.2. Randomized Treatment Regimens/Dosage and Administration.....	24
7.3. Packaging	25
7.4. Subject Numbers	25
7.5. Labeling.....	26
7.6. Blinding	26
7.7. Drug Accountability: Shipping, Receipt, Storage, Dispensing and Return of Study Drug	26
8. Prior, Concomitant, and Prohibited Medications and Treatments	27
9. Study Procedures	27
9.1. Screening and Enrollment/Baseline Visit (Visit 1)	28

9.1.1. Informed Consent	28
9.1.2. Demographic Information, Medical & Surgical History, and Physical Exam	28
9.1.3. Subject Assessment of Symptoms.....	28
9.1.4. Laboratory Tests and Specimen Collections	28
9.1.5. Pelvic Examination and Specimen Collections.....	28
9.1.6. Gram Stain Processing and Interpretation	30
9.1.7. Diagnosis for Infection Study Enrollment	30
9.1.8. Randomization and Drug Dispensing	30
9.1.9. Subject Instructions.....	30
9.2. Test of Cure Visit (Visit 2).....	31
9.2.1. Review of Diary	31
9.2.2. Inquire Regarding Compliance	31
9.2.3. Time to Symptom Resolution/Reoccurrence	32
9.2.4. Subject Assessment of Symptoms.....	32
9.2.5. Laboratory Tests and Specimen Collections	32
9.2.6. Pelvic Examination and Specimen Collections.....	32
9.2.7. Inquire Regarding Adverse Events	33
9.2.8. Inquire Regarding Changes in Concomitant Medication	33
9.2.9. Collection of Unused Study Drug	33
9.2.10. Assessment of Clinical Status: Need for Additional Treatment	33
9.2.11. Determination of Cure or Failure of Subject's Enrolled Infection	33
9.2.12. Subject Instructions	34
9.3. Follow Up Visit (Visit 3).....	34
9.3.1. Inquire Regarding Compliance	35
9.3.2. Subject Assessment of Symptoms.....	35
9.3.3. Laboratory Tests and Specimen Collections	35
9.3.4. Pelvic Examination and Specimen Collections.....	35
9.3.5. Inquire Regarding Adverse Events	35
9.3.6. Inquire Regarding Changes in Concomitant Medication	35
9.3.7. Assessment of Clinical Status: Need for Additional Treatment	36
9.3.8. Distribution of Subject Satisfaction Survey.....	36
9.4. Unscheduled Visits	36
10. Adverse Events and Safety Reporting.....	36
10.1. Definition of Adverse Event/Adverse Reaction/Suspected Adverse Reaction	36
10.2. Protocol-Specific Adverse Event Considerations	37
10.3. Definition of Serious Adverse Events (SAE)	37
10.4. Definition of Unexpectedness.....	38
10.5. Documentation of Adverse Events	38
10.6. Severity Criteria	38
10.7. Relatedness Criteria	38
10.8. Serious Adverse Event Reporting	39
10.9. Safety Reporting to Investigators, IRBs, and Regulatory Authorities by Curatek.....	39
11. Statistical Methods.....	40
11.1. General Methods	40
11.2. Study Conduct Summaries	41
11.3. Analysis Populations	41
11.4. Determination of Sample Size	42

11.5. Handling of Missing Data	43
11.6. Efficacy Analyses	43
11.6.1. Primary Efficacy Analysis.....	43
11.6.2. Secondary Efficacy Analyses.....	44
11.7. Safety Analysis.....	44
11.7.1. Adverse Events.....	45
11.7.2. Laboratory Assessments.....	45
11.7.3. Vital Signs.....	46
11.7.4. Physical Exams.....	46
12. Data Handling and Record Keeping	46
12.1. Source Documents	46
12.2. Case Report Forms.....	46
12.3. Record Retention.....	47
12.4. Data Management	47
13. Study Management	47
13.1. Monitoring and Source Data	47
13.2. Protocol Adherence	48
13.3. Protocol Amendments	48
13.4. Protocol Violations	48
13.5. Quality Assurance and Regulatory Agency Audits	48
14. Ethical and Regulatory Considerations	48
14.1. Ethical Considerations	49
14.2. Institutional Review Board.....	49
14.3. Informed Consent.....	49
14.4. Delegation Log	50
14.5. Reports and Publications	50
14.6. Public Posting of Trial Information.....	50
14.7. Subject Release from the Study.....	50
14.8. Sponsor Discontinuation of Study.....	50
15. References	51

List of Appendices

Appendix A: Schedule of Procedures.....	53
Appendix B: Instructions for Subjects.....	55
Appendix C: Instructions for Using Study Drug	56
Appendix D: Subject Diary	57
Appendix E: Subject Satisfaction Survey	59

3. Background and Rationale

3.1. Bacterial Vaginosis

Bacterial vaginosis (BV) is one of the most common vaginal disorders in women of reproductive age affecting almost a third of United States (US) women.¹ Subjects with BV often complain of unpleasant or malodorous vaginal discharge. Some women experience discomfort or irritation. Generally there is a lack of inflammation associated with BV.²

The vaginal microbiome is complex and in healthy women various *Lactobacillus* species dominate the ecosystem.³ Originally referred to as “non-specific vaginitis,” the search for a causative organism in BV led the condition to be called, at various times, *Haemophilus vaginalis* vaginitis,⁴ *Corynebacterium vaginalae* vaginitis⁵ and *Gardnerella vaginalis* vaginitis.⁶ More recent studies have suggested that rather than a single causative organism, BV is characterized by a shift in the vaginal flora whereby the usual populations of vaginal *Lactobacilli* decline and are replaced by an overgrowth of facultative and anaerobic organisms including *Gardnerella vaginalis*, *Atopobium*, *Prevotella*, *Bacteroides*, *Peptostreptococcus* and *Mobiluncus* species,⁷ as well as *Mycoplasma hominis*,⁸ *Leptotrichia amnionii*, and *Eggerthella* species.⁹ More recently, broad-range 16S rRNA gene PCR and pyrosequencing of vaginal samples from women with confirmed BV have shown that there is a large diversity of species and that no individual species is universally present.⁹

The apparent lack of a single causative organism has made the diagnosis of BV somewhat more difficult compared to other vaginal infections. In current medical practice, the diagnosis is generally made based on the following clinical signs, which are known as the “Amsel criteria”¹⁰:

- Presence of a thin, homogeneous vaginal discharge
- Vaginal pH > 4.5
- Positive potassium hydroxide (KOH) “whiff test” indicating presence of volatile amines in the vaginal secretions
- Presence of “clue cells” on microscopic examination of saline “wet mount” of vaginal secretions. Clue cells are epithelial cells whose borders are obscured by the presence of numerous bacteria clinging to the cell.

Another method used to diagnose BV is interpretation of a vaginal Gram stain according to the “Nugent criteria.”¹¹ According to this method bacteria are counted and scored based on:

- Relative absence of *Lactobacillus* morphotypes
- Presence of small Gram-variable coccobacilli and small gram-negative rods (indicative of *Gardnerella* and *Prevotella/Bacteroides* species)
- Presence of small curved Gram-variable rods (indicative of *Mobiluncus* species)

The scores in these three categories are added to give a composite score that categorizes flora as normal (score 0-3), intermediate (score 4-6) or BV (score 7-10).

Current available treatments for BV in the US include oral and intravaginal forms of metronidazole and clindamycin¹² as well as oral tinidazole. Intravaginal preparations may have fewer adverse events compared to systemic medications. Depending on the criteria used to evaluate efficacy, available treatments cure BV in approximately 25-55% of subjects. The relative efficacy appears to be similar for all therapies. One disadvantage of these agents is the overgrowth of yeast following therapy, which

seems to occur in approximately 10% of subjects.¹³ This may be due to the fact that when bacterial populations are eliminated yeast has a better chance to overgrow.

Metronidazole has been used orally in doses of 500 mg twice daily for 7 days. A 750 mg tablet used for 7 days is also approved. Intravaginal metronidazole is available as a 0.75% gel that is applied once or twice a day for 5 days. Intravaginal administration reduces systemic exposure to the drug and may decrease the incidence of side effects.

Clindamycin is also used orally, usually in doses of 300 mg twice daily for 7 days. There are three intravaginal clindamycin products approved in the US: a 2% cream used once daily for 3 or 7 days, a 100 mg vaginal suppository used once daily for 3 days, and a single dose 2% cream.

Tinidazole is a nitroimidazole similar to metronidazole that is currently marketed in the US as an oral medication for the treatment of vaginal trichomoniasis and other protozoal infections as well as BV.

3.2. Vulvovaginal Candidiasis

Vulvovaginal candidiasis (VVC), also known as yeast vaginitis or moniliasis, is another common vaginal infection.¹⁴ It has been estimated that 75% of women will experience at least one episode of VVC.¹⁵

The primary symptoms of VVC are itching, burning, and irritation of the vagina and/or vulva. The associated signs include erythema, edema and excoriation. *Candida albicans* is the causative pathogen in the majority of cases. Other *Candida* species such as *C. tropicalis* and *C. glabrata* may also be involved, particularly in recurrent infection.¹⁶

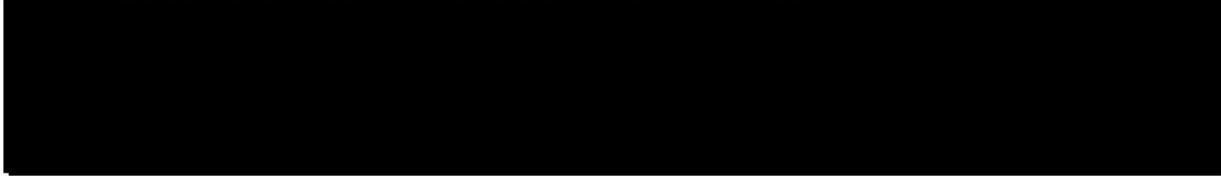
Diagnosis of VVC is made based on subject complaints, office wet mount microscopy and yeast cultures. However, there has been shown to be a lack of correlation between self-reported symptoms (vaginal/vulvar pain, burning, itching, and dyspareunia), wet mount microscopy and yeast culture. Diagnosis based on cultures for *Candida* has been shown to be much more accurate,^{17,18} and culture is considered to be the “gold standard” for diagnosis and determination of cure. One recent study showed patient symptoms in particular were a poor predictor of yeast infections compared to culture, with a high sensitivity (90%) but a very low specificity (7%).¹⁹

Current recommended treatments for VVC include intravaginal “azoles” (such as miconazole, clotrimazole, butoconazole, tioconazole and terconazole) and oral fluconazole. All of these agents, except for terconazole and fluconazole, are also available in non-prescription, over-the-counter formulations in the US. A three-day regimen of terconazole 0.8% cream is one of the treatment options for VVC recommended by the Centers for Disease Control.¹²

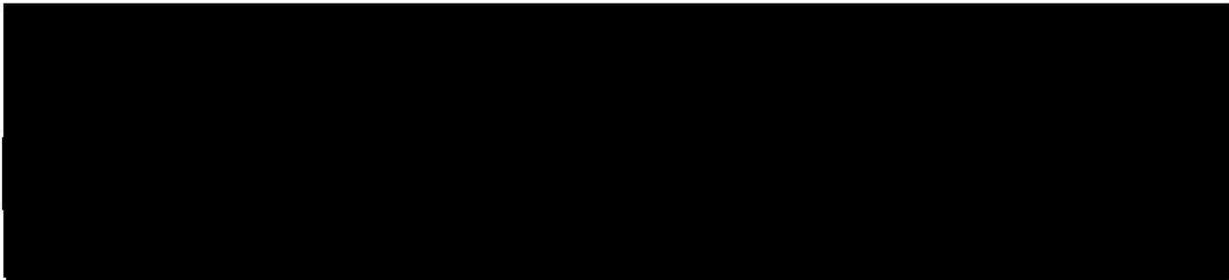
3.3. Rationale for Metronidazole 0.9% Vaginal Gel (BV Gel)

[REDACTED]

3.4. Rationale for Terconazole 0.8% Vaginal Gel (VVC Gel)



3.5. Rationale for Combination Metronidazole 0.9% Gel and Terconazole 0.8% Vaginal Gel (Combo Gel)



3.6. Rationale for Comparators in Each Infection Study

For the BV Study the gel vehicle is used as a placebo in order to provide a meaningful analysis and estimate of the true effect of the metronidazole 0.9% component of the gel. Any potential beneficial effects of the gel base, such as pH alteration, will be present in both arms of the study.

For the VVC Study the gel vehicle is used as a placebo in order to provide a meaningful analysis and estimate of the true effect of the terconazole 0.8% component of the gel. Any potential beneficial effects of the gel base, such as local soothing, will be present in both arms of the study.

For the Mixed Infection Study the Combo Gel is being compared to metronidazole 0.9% gel and to terconazole 0.8% gel (the single entity gels). This approach is required to establish the effect of the combination compared to the two drugs separately and thereby justify the combination.

Subjects who receive placebo gels in the BV study and the VVC study, and subjects who receive single entity gels in the Mixed Infection study will presumably not be getting effective treatment. The investigator should be alert to any symptoms the subject is experiencing after treatment, particularly at Visit 2, and not hesitate to bring symptomatic subjects back to the clinic for an unscheduled visit at any

time. The subject should also be instructed that she may notify the investigator of any bothersome symptoms, as well as request alternative treatment, at any time.

4. Study Design

This is a multi-center, phase III trial, comprised of three studies, each designed to test the safety and efficacy of a different investigational product, for a specific vaginal infection/indication. They are:

1. Bacterial Vaginosis (BV) Study: A randomized, double-blind, parallel-group, placebo-controlled study to test the safety and efficacy of BV Gel (0.9% metronidazole gel) for the treatment of BV
2. Vulvovaginal Candidiasis (VVC) Study: A randomized, double-blind, parallel-group, placebo-controlled study to test the safety and efficacy of VVC Gel (0.8% terconazole gel) for the treatment of VVC
3. Mixed Infection (Concurrent BV and VVC) Study: A randomized, double-blind, parallel-group, active-controlled study to test the safety and efficacy of Combo Gel (0.9% metronidazole gel and 0.8% terconazole gel) for the treatment of Mixed Infection

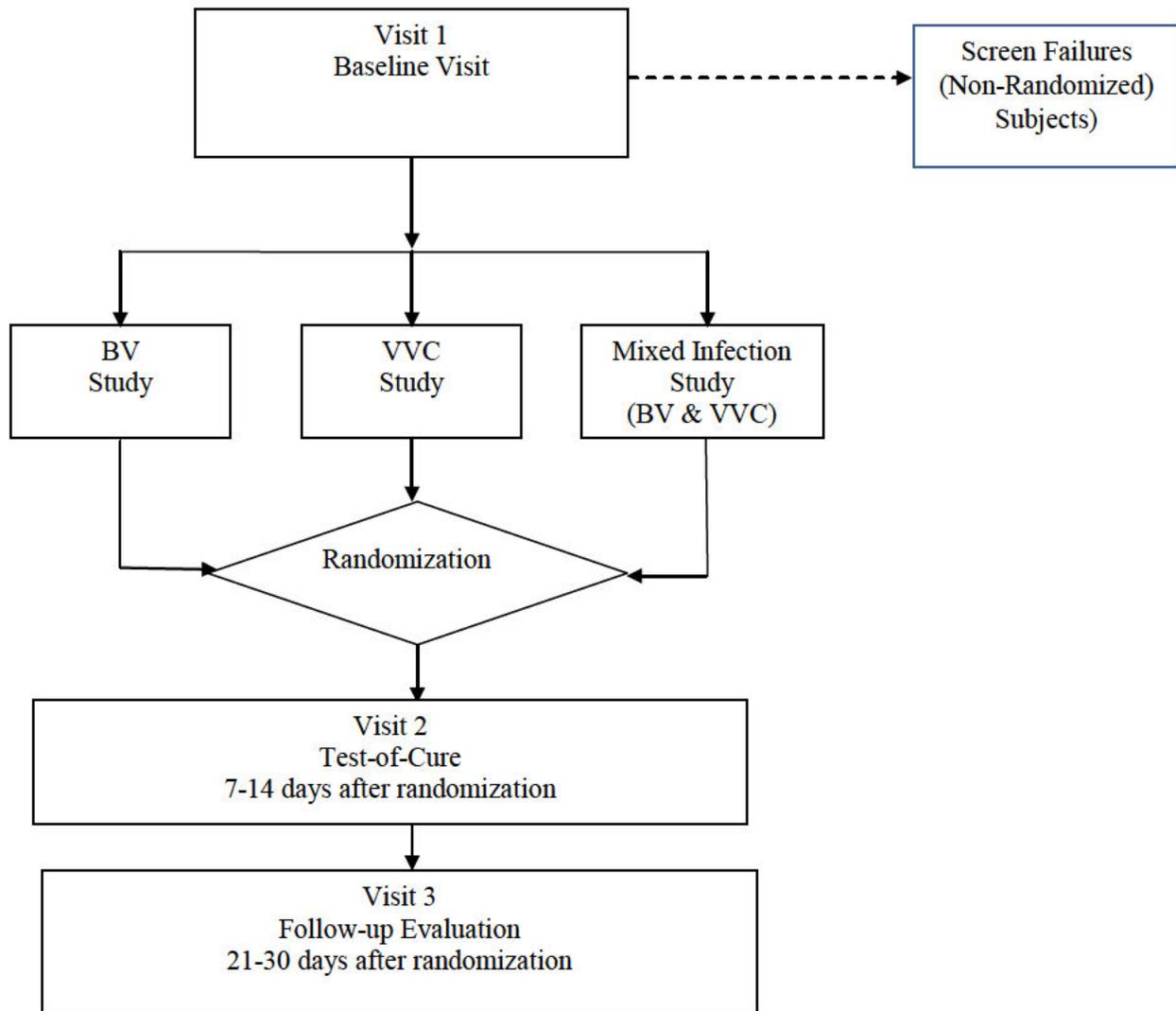
All study medication is intravaginal and will be dosed as one applicatorful for three consecutive days.

Subjects who sign an informed consent form (ICF), are diagnosed with BV, VVC, or Mixed Infection, and meet eligibility requirements will be enrolled into the appropriate infection study and subsequently randomized to treatment based on clinical diagnosis at the screening and enrollment/baseline visit (Visit 1). BV subjects will be entered into the BV Study, VVC subjects will be entered into the VVC Study, and concurrent BV and VVC (Mixed Infection) subjects will be entered into the Mixed Infection Study.

All subjects will be asked to return for a test of cure visit (Visit 2) 7-14 days after randomization. If a subject is menstruating on the day of the scheduled visit, she should be rescheduled to return 24 hours after completion of menses. Subjects who in the opinion of the investigator/clinician require additional treatment for vaginal discomfort/symptoms and subjects who self-medicated for vaginal discomfort/symptoms, will be terminated from the study. All other subjects will return for a follow-up evaluation visit (Visit 3) 21-30 days after randomization.

Study procedures will be identical in all three infection studies with the exception of safety labs (i.e. Hematology: complete blood count (CBC) with differential and Chemistry: blood urea nitrogen (BUN), Creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and bilirubin) which will only be obtained at Visit 1 and Visit 2 on subjects entered into the Mixed Infection Study. There will be one case report form (CRF) for each subject. The CRF will be the same for all three infection studies. Analysis of safety and efficacy will be performed separately for each investigational product.

A schematic of the study design follows.



5. Study Objectives and Endpoints

5.1. Primary Objectives

1. BV Study: Evaluate the safety and efficacy of BV Gel in the treatment of bacterial vaginosis (BV)
2. VVC Study: Evaluate the safety and efficacy of VVC Gel in the treatment of vulvovaginal candidiasis (VVC)
3. Mixed Infection Study: Evaluate the safety and efficacy of Combo Gel in the treatment of concurrent BV and VVC (Mixed Infection)

5.2. Primary Efficacy Endpoints and Evaluations

1. BV Study: BV cure rate, with cure defined as normal/physiologic discharge,^e negative whiff test, and < 20% clue cells (i.e. clinical cure)
2. VVC Study: VVC cure rate, with cure defined as resolution of all signs and symptoms attributable to VVC (i.e. clinical cure)
3. Mixed Infection Study: Mixed Infection cure rate, with cure defined as BV cure (i.e. BV clinical cure) **AND** a VVC cure (i.e. VVC clinical cure)

Primary efficacy endpoint evaluations will occur at the test-of-cure Visit 2.

If a subject requires additional treatment for vaginal discomfort/symptoms (i.e. a BV subject requiring treatment for BV, a VVC subject requiring treatment for VVC or a Mixed Infection subject requiring treatment for BV and/or VVC) prior to or at Visit 2, the subject will be considered a treatment failure. These subjects will be evaluable for the intent-to-treat (ITT), modified intent-to-treat (mITT) and the per-protocol (PP) population analyses, providing all other evaluability criteria for these population groups have been met.

Additionally, if a subject self-medicates herself for vaginal discomfort/symptoms at any time prior to Visit 2, the subject will be considered a treatment failure.^f If this occurs, the subject will remain evaluable for the ITT and the mITT analyses, but will be non-evaluable for the PP analysis.

5.3. Secondary Endpoints and Evaluations

1. BV Study: BV clinical and Nugent score cure rates alone and combined; changes/improvements in Amsel criteria and Nugent scores; time to resolution of vaginal symptoms
2. VVC Study: VVC clinical (i.e. resolution of all signs and symptoms attributable to VVC) and mycologic cure rates (i.e. negative *Candida* on culture) alone and combined; changes/improvements in signs and symptoms scores ; eradication (or persistence) of individual fungal species; time to resolution of vaginal symptoms
3. Mixed Infection Study: BV clinical and Nugent score cure rates alone and combined; changes/improvements in Amsel criteria and Nugent scores; VVC clinical and mycologic cure rates alone and combined; changes/improvements in signs and symptoms scores; eradication or persistence of individual fungal species; time to resolution of vaginal symptoms

Secondary endpoint evaluations will occur at Visits 2 and 3 and will utilize criteria appropriate to the subject's entry diagnosis (i.e. study subject was enrolled in).

6. Selection of Study Population

6.1. Recruitment Procedures

Sites will recruit participants through various mechanisms, including but not limited to recruitment from an investigator's own private/clinic patients, provider referrals, Institutional Review Board (IRB)

^e In the event a BV subject has discharge consistent with VVC (i.e. white, creamy, and curdy [cottage cheese like] adherent to the epithelium), the subject will be considered a BV cure providing all other criteria for BV cure (and evaluability) are met and the subject has a positive yeast culture.

^f Self-administration of therapy includes prescription and over-the-counter (OTC) antimicrobial, anti-fungal, analgesics, or steroid treatments.

approved advertisements and patient registries. The trial will be conducted at approximately 40 investigative sites, each of which is expected to contribute an approximately equal number of subjects. However, differences in subject availability may result in one site enrolling more subjects than another.

Subjects will be enrolled until approximately 116 evaluable BV subjects, 100 evaluable VVC subjects, and 189 evaluable Mixed Infection subjects, per protocol population, complete the trial. [REDACTED]

[REDACTED] Once the total number of evaluable subjects in a study is reached, that study will be closed and the remaining studies will continue to enroll subjects.

6.2. Registration Procedures

All subjects who sign an informed consent and are screened for enrollment into one of the three infection studies will be entered into the interactive voice response (IVR)/interactive web response (IWR) system.

6.2.1. Screen Failures

If a subject does not meet eligibility based on baseline clinical criteria or withdraws consent prior to study randomization, the subject will be considered a screen failure. A case report form should not be filled out; however the reason the subject screen failed should be documented in the subject's source notes. Screen failures will be tracked in the IVR/IWR system and a screening and enrollment log will be maintained at each site.

6.2.2. Subject Identification Log

The investigator will maintain a subject identification log throughout the trial to allow for easy identification of each subject during and after the trial. This log will be reviewed by the study monitor for completeness but will be treated as confidential. As such, no copy will be made and it will only be filed at the investigative site.

6.3. Inclusion/Exclusion Criteria

To be enrolled into one of the three infection studies, subjects must meet all eligibility requirements as specified in the inclusion/exclusion criteria listed below. Since some of the tests for determining eligibility will not be available at the baseline visit (i.e. tests for *Trichomonas vaginalis*, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, active *Herpes simplex* virus; Nugent score, and yeast culture), enrollment will be based on clinical criteria (i.e. Amsel criteria and/or signs and symptoms of VVC including wet mount microscopy). Subjects may only be enrolled under this protocol once.

6.3.1. Inclusion Criteria

- **Clinical diagnosis of BV** based on the presence of ALL of the following:
 - Amsel criteria (all four of the following criteria must be present):
 1. Abnormal vaginal discharge consistent with BV (i.e. off-white [milky or gray], thin, homogeneous discharge)^g
 2. Vaginal secretion pH of > 4.5
 3. A fishy odor of the vaginal discharge with the addition of a drop of 10% KOH (i.e. a positive "whiff test")

^gSubjects with Mixed Infection (i.e. concurrent BV and VVC) may have an abnormal discharge consistent with BV, consistent with VVC (i.e. white, creamy, and curdy [cottage cheese like] adherent to the epithelium), or an abnormal discharge of varying characteristics with relation to odor, color, and consistency.

4. Presence of clue cells $\geq 20\%$ of the total epithelial cells on microscopic examination of the saline wet mount
- AND**
- Nugent score of ≥ 4 based on baseline Gram stain slide

AND/OR

- **Clinical diagnosis of VVC** based on the presence of ALL of the following:
 - A composite signs and symptoms score ≥ 2 based on rating the following six vaginal/vulvar signs and symptoms on a severity scale, where absent =0, mild =1, moderate =2 and severe =3:
 1. Itching
 2. Burning
 3. Irritation
 4. Edema
 5. Erythema
 6. Excoriation
 - Presence of yeast forms (hyphae/pseudohyphae) or budding yeasts seen on microscopic examination of a KOH prepared slide of vaginal secretions
- AND**
- **Mycologic diagnosis of VVC** based on positive culture for *Candida* species

AND

- At least 12 years of age
- Capable of providing written informed consent; if a minor, capable of assent with parent/legal guardian available to provide written informed consent
- Willing to begin treatment within 2 days of the baseline Visit (Visit 1)
- Currently not menstruating and not anticipating menses during treatment
- Willing to abstain from sexual intercourse through Visit 2 and have their partner use a non-lubricated condom within the preceding 48 hours of Visit 3 if sexual intercourse occurs
- Willing to abstain from using intravaginal/vulvovaginal products (e.g. feminine hygiene products such as douches and deodorants; contraceptive products such as diaphragms, spermicidal creams, gels, and foams; vaginal lubricants, moisturizers, and hormonal suppositories and creams such as Vagifem®, Estrace® and Premarin® cream; and tampons etc.) through Visit 2 and within 48 hours of Visit 3
- Willing to abstain from alcohol and propylene glycol ingestion during treatment and for 1 day thereafter
- If heterosexually active, subject must be post-menopausal for ≥ 1 year, surgically sterile (i.e. hysterectomy, bilateral oophorectomy, or bilateral tubal ligation), sexually active with a male partner who is surgically sterile (i.e. vasectomy), or practicing an acceptable form of birth control (i.e. oral contraceptives, contraceptive injections, contraceptive patch, condoms, or intrauterine device [IUD]) for at least one month before study entry and agree to continue the contraceptive method for the duration of the study. If sexually abstinent, subjects must agree to continue abstinence or use an acceptable method of birth control should sexual activity commence during the study.
- Willing and capable of cooperating to the extent and degree required by the protocol
- Negative urine pregnancy test (unless subject is surgically sterile or post-menopausal ≥ 1 year)

6.3.2. Exclusion Criteria Applicable to all Infection Studies

- Other infectious causes of vulvovaginitis (e.g. *Trichomonas vaginalis*, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, active *Herpes simplex* virus or genital warts)
- Subject has used systemic (oral, intravenous [IV], or intramuscular [IM]), intravaginal/vulvovaginal antifungal, antimicrobial, or corticosteroid therapy within 14 days of study enrollment
- Subject is currently taking or has taken disulfiram therapy within 14 days of study enrollment
- Subject is currently on lithium, coumarin anticoagulants (e.g. warfarin), or immunosuppressive therapy
- Subject is expected to require the concomitant use of prohibited medications/products while enrolled in the study
- Subject will require treatment for cervical intra-epithelial neoplasia (CIN) or cervical carcinoma while enrolled in the study
- Nursing mother
- Use of any investigational drug within 30 days of enrollment or plans to use other investigational products while enrolled in the study
- Known primary or secondary immunodeficiency
- Presence of any condition or illness, including vulvar and vaginal conditions, that in the opinion of the investigator would preclude accurate evaluation of the subject's condition and/or confound the interpretation of the subject's treatment response
- History of hypersensitivity to metronidazole or other nitroimidazoles; terconazole or other triazoles; parabens; or any other ingredient/component of the formulations

Subjects who meet criteria for BV only will be entered into the BV Study and randomized to a BV treatment, subjects who meet criteria for VVC only will be entered into the VVC Study and randomized to a VVC treatment, and subjects who meet criteria for both BV and VVC will be entered into the Mixed Infection Study and randomized to treatment for Mixed Infection.

7. Study Drug

7.1. Drug Supplies

Curatek Pharmaceuticals, LLC, Elk Grove Village, IL will supply BV Gel (0.9% metronidazole), VVC Gel (0.8% terconazole), Combo Gel (0.9% metronidazole and 0.8% terconazole), and Placebo Gel for this study. All of these gels will be manufactured at [REDACTED] and packaged in identical 30 gram tubes.

7.2. Randomized Treatment Regimens/Dosage and Administration

Randomization, determined by a computer generated randomization scheme, will be used to avoid bias in the assignment of subjects to treatment and to enhance the validity of statistical comparisons between treatments.

All eligible subjects will be randomized at the baseline visit (Visit 1) utilizing an interactive voice response (IVR)/interactive web response (IWR) system. Subjects in the BV or VVC study will be randomly assigned to one of two treatment groups in a 1:1 ratio while subjects in the Mixed Infection study will be randomized to one of three treatment groups in a 1:1:1 ratio. All treatments, regardless of study, consist of three doses, to be administered by vaginal applicator at bedtime for three consecutive days.

Subjects will be randomized to treatment as follows:

- Subjects diagnosed with BV will be randomized to receive treatment with either BV Gel (0.9% metronidazole gel) or Placebo Gel. Each 5-gram dose of BV Gel contains 45 mg of metronidazole for a total dose of 135 mg of metronidazole.
- Subjects diagnosed with VVC will be randomized to receive treatment with either VVC Gel (0.8% terconazole) or Placebo Gel. Each 5-gram dose of VVC Gel contains 40 mg of terconazole for a total dose of 120 mg of terconazole.
- Subjects diagnosed with Mixed Infection will be randomized to receive treatment with BV Gel, VVC Gel, or Combo Gel (0.9% metronidazole and 0.8% terconazole). Each 5-gram dose of the Combo Gel contains 45 mg of metronidazole and 40 mg of terconazole for a total dose of 135 mg of metronidazole and 120 mg of terconazole.

7.3. Packaging

BV Gel, VVC Gel, Combo Gel, and Placebo Gel will have identical primary, secondary, and tertiary packaging. Each tube of study drug will be placed in a box (secondary packaging) with three disposable applicators. Each box will then be placed inside another larger box (tertiary packaging), containing study instructions (Appendix B), instructions for the use of study drug (Appendix C), condoms, a subject diary (Appendix D), and return packaging to be utilized when drug is returned (i.e. the drug tube with any remaining unused drug inside). The outer box will be sealed and labeled with a two-part label, as described in Section 7.5. The entire contents of the boxes will comprise a study Drug Kit.

Each Drug Kit will be labeled (as described in Section 7.5, Labeling) with a unique Drug Kit number, previously determined by a computer generated randomization scheme (as described in Section 7.2, Randomized Treatment Regimens/Dosage and Administration), that dictates the treatment assignment for each subject. Both subject numbers and corresponding Drug Kit numbers will be assigned at Visit 1 via the IVR/IWR system at the time of randomization.

Drug Kit demonstration boxes will be provided to each site for subject instructions and education. The investigator/clinician will use the demonstration kit to show each subject how to puncture the seal on the drug tube, fill the applicators and administer the gel. Subjects will be instructed to use one applicatorful of study drug at bedtime for three consecutive days. All subjects should place their drug tube in the return packaging provided, seal the packaging and return it to the study staff at the next scheduled visit (as described in Section 7.6, Blinding).

Instructions for completing the diary will be reviewed with the subject. The diary will track study drug dosing, study compliance, symptom resolution/reoccurrence, and adverse events. Subjects will be instructed to return the completed diary at their next scheduled visit (Visit 2).

7.4. Subject Numbers

Subject numbers will have a two-digit prefix representing the unique site number followed by another three digit number. Subject numbers will be assigned at the baseline visit via the interactive voice response (IVR)/interactive web response (IWR) system to all subjects who sign an informed consent. Subjects who meet enrollment criteria and are entered into an infection study will maintain the same subject number throughout enrollment.

7.5. Labeling

All study drug tubes will have the lot number printed on them. The lot numbers will be covered by opaque labels containing the following information:

- Protocol number
- Unique Drug Kit number
- Instructions: “Insert one applicatorful of drug in the vagina at bedtime for 3 consecutive days.”
- Caution statement – “Caution: New Drug-Limited by Federal (United States) law to investigational use.”
- Storage statement: “Store at 20°-25° C (68°-77° F); excursions permitted to 15°-30° C (59°-86° F).”
- Sponsor identification: Curatek Pharmaceuticals, LLC Elk Grove Village, IL 60007

A two-part tear-off label will be attached to the sealed outer box of the Drug Kits. Both parts of this label will have matching information: the protocol number, the unique Drug Kit number, a storage statement, sponsor identification, and a place to enter the subject’s initials and subject number at the time of Drug Kit dispensation.

7.6. Blinding

The investigator/study staff will be blinded to the therapy each subject receives. Blinding will be achieved by identical primary, secondary, and tertiary packaging of study drugs (i.e. Drug Kits) for all treatment arms in all infection studies. All infection studies will be double-blind.

To maintain investigator/study staff blinding upon return of study drug, subjects will be instructed to place their unused drug inside the opaque packaging provided and return it sealed at their next scheduled visit.

Investigators will not receive randomization codes. The codes will be maintained within the IVR/IWR system which investigators will have the capability of breaking for an individual subject if necessary. The blind should only be broken if a specific emergency treatment would be dictated by knowing the treatment assignment of the subject. In such instances, the investigator must first notify Curatek. If Curatek is unable to be contacted, the investigator may telephone the IVR/IWR system to identify the subject’s treatment assignment. In this instance, Curatek must be notified as soon as possible. Details regarding the un-blinding including the date, time, and reason for un-blinding must be documented in the subject’s source notes and the CRF.

7.7. Drug Accountability: Shipping, Receipt, Storage, Dispensing and Return of Study Drug

Curatek/Curatek’s designee is responsible for shipping and supplying each investigator with study drug (i.e. Drug Kits) and study supplies. No drug will be shipped until all required regulatory documentation has been obtained (i.e. IRB approval of the protocol and informed consent, Form FDA 1572, investigator curriculum vitae (CV)(s) and financial disclosure(s) etc.). All shipments of drug will contain a packing slip/shipping invoice which must be used to inventory the shipment and maintained in the regulatory binder. Confirmation of receipt of the shipment must be made via the IVR/IWR system.

The investigator/designee is responsible for ensuring that the study drug is stored in a secure, limited access area at controlled and monitored room temperature (20°-25° C [68°-77° F]; excursions permitted to 15°-30° C [59°-86° F] *see USP controlled room temperature*). A temperature log must be maintained and will be reviewed by the monitor during monitoring visits.

The investigator/designee will be responsible for accountability of study drug. Documentation of drug accountability must be maintained and kept current throughout the study and includes the receipt, subject dispensation, subject return of unused drug, and the return of unused and never dispensed drug to Curatek/Curatek's designee. During the study, drug accountability records will be reviewed by the monitor and at the end of the study the completed records will be maintained in the trial master file (TMF).

Subjects will be instructed to return their unused drug as described in Section 7.6 above to the study site at Visit 2. The return of unused drug is required to complete drug accountability and for subsequent return, weighing, and destruction of study drug by Curatek/Curatek's designee. Subjects will also be asked to return their completed diaries at Visit 2 so that study drug administration/compliance can be confirmed.

8. Prior, Concomitant, and Prohibited Medications and Treatments

Subjects receiving drug therapy for conditions other than BV and/or VVC may continue those medications during the study, provided they are not exclusionary or prohibited medications. New medications for the treatment of conditions other than BV and/or VVC may be initiated during the study, provided they are not prohibited medications and would not interfere with the evaluation of the study assessments. All concomitant medication use will be documented in the subject's source documents.

Prohibited medications during the entire study include:

- systemic, intravaginal/vulvovaginal antifungal, antimicrobial (i.e. other than study drug), and corticosteroid drugs
(Note: Inhaled, intranasal, intra-articular, and/or topical steroids [provided they are not intravaginal/vulvovaginal] are not prohibited.)
- immunosuppressive therapy

Prohibited medications during treatment and for two days thereafter:

- disulfiram, lithium, and coumarin anticoagulants (e.g. warfarin)

Prohibited products through Visit 2 and within 48 hours of Visit 3 include:

- Intravaginal/vulvovaginal product use (e.g. feminine hygiene products such as douches and deodorants; contraceptive products such as diaphragms, spermicidal creams, gels, and foams; vaginal lubricants, moisturizers, and hormonal suppositories and creams such as Vagifem®, Estrace® and Premarin® cream; and tampons)
- Following Visit 2 and for the remainder of study enrollment, subjects will be encouraged to refrain from the use of intravaginal/vulvovaginal products.

Additional restrictions:

- Alcoholic beverages and propylene glycol ingestion are prohibited during treatment and for 1 day thereafter.

9. Study Procedures

The following sections describe the procedures to be completed at each visit. Whenever possible, subjects should be evaluated by the same investigator/clinician at their baseline and follow-up visits.

Information obtained should be recorded in source documents and subsequently transcribed onto the CRF. A schedule of procedures is provided in Appendix A.

9.1. Screening and Enrollment/Baseline Visit (Visit 1)

Inclusion/exclusion criteria will be reviewed and the following procedures will be performed during the baseline visit to determine subject eligibility for infection study enrollment and to establish baseline parameters.

9.1.1. Informed Consent

All subjects must give written informed consent prior to performing any study-related activities. Assent for subjects between 12 and 18 years will be obtained per IRB requirements. Refer to Section 14.3. Informed Consent.

9.1.2. Demographic Information, Medical & Surgical History, and Physical Exam

Demographic information, a medical and surgical history, and physical examination inclusive of vital signs will be performed on each subject. The subject's contraceptive, obstetric, and gynecological history will be obtained. Concomitant medication usage (i.e. current and within 30 days of enrollment) as well as treatments for BV and/or VVC infections within the past year will be obtained.

9.1.3. Subject Assessment of Symptoms

Subjects will be asked to rate their current vulvovaginal symptoms of itching, burning, and irritation as absent=0, mild=1, moderate=2 or severe=3. The sum of the symptom score will be added to the vulvovaginal signs score obtained during the pelvic examination to determine a combined symptom and sign severity score. This combined score must be ≥ 2 in order to meet entry criteria for enrollment into the VVC or Mixed Infection Study.

9.1.4. Laboratory Tests and Specimen Collections

The lab tests listed below will be obtained at the baseline visit (Visit 1).

- Urine pregnancy test for all women of child bearing potential
- Papanicolaou smear (if subject is ≥ 21 years old and a Pap smear was not done within the past 3 years)
- Tests for *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Trichomonas vaginalis*
- Culture for *Herpes simplex* (only if suspected)
- Vaginal culture for *Candida* species
- Vaginal Gram stain
- CBC with differential and blood chemistries (i.e. BUN, Creatinine, ALT, AST, ALP, and bilirubin) for subjects enrolled in the Mixed Infection Study

9.1.5. Pelvic Examination and Specimen Collections

A non-lubricated speculum (tap water rinse acceptable) should be used during the pelvic examination. Components of the pelvic examination should include the following:

- Visual inspection: rule out lesions caused by *Herpes simplex* virus or human papilloma virus (i.e. genital warts)
- Vulvovaginal signs rating: rate the degree of vulvovaginal edema, erythema, and excoriation as absent = 0, mild = 1, moderate = 2 or severe = 3. The sum of these ratings will be added to the vulvovaginal symptoms score given by the subject to determine a combined symptom and sign

severity score. This total score must be ≥ 2 in order to meet entry criteria for enrollment into the VVC or Mixed Infection study.

- Vaginal discharge characterization: By visual examination, characterize vaginal discharge in accordance with the descriptions below.
 - Normal/physiologic: normal discharge may vary in appearance and consistency depending on the menstrual cycle;
 - Abnormal: consistent with BV (i.e. off-white [milky or gray], thin, homogeneous discharge);
 - Abnormal: consistent with VVC (i.e. white, creamy, and curdy [cottage cheese like] adherent to the epithelium);
 - Abnormal: consistent with Mixed Infection (i.e. discharge of varying characteristics with relation to odor, color, and consistency)
- pH measurement: Obtain a vaginal pH measurement with the pH indicator strips provided. Take care to avoid contacting cervical mucus with the sample.
- Whiff test and KOH and saline wet mounts
 - Swab lateral vaginal walls with a cotton-tipped applicator and place a liberal amount of discharge on each of 2 glass slides.
 - Mix 2 drops of 10% KOH with the discharge on one slide and immediately determine if a fishy, amine-like odor is present.
 - Mix 2 drops of 0.9% saline with the discharge on the other slide and place cover slips over both slides.
 - Examine both slides under a light microscope at both 100 X and 400 X magnifications.
 - On the KOH slide note presence or absence of yeast organisms (hyphae, pseudohyphae, and/or budding yeast). The presence of yeast is required to meet entry criteria for the VVC or Mixed Infection Study. Several fields should be examined.
 - On the saline slide note presence or absence of clue cell and motile trichomonads. Multiple representative fields should be examined and the ratio of clue cells to epithelial cells determined. Clue cells will be identified as epithelial cells with such a heavy coating of bacteria that their peripheral borders are obscured. Clue cells must be $\geq 20\%$ of vaginal epithelial cells in order to meet entry criteria for the BV or Mixed Infection study.
- Vaginal *Candida* culture: Obtain a *Candida* culture as specified in the central laboratory manual utilizing the collection and shipment supplies provided. Cultures should be shipped on the day of collection; unless otherwise specified for weekends and holidays.
- Vaginal Gram stain: Obtain and prepare a slide for the central lab to Gram stain as specified below.
 - Swab lateral vaginal walls with a cotton-tipped applicator. Place a moderate amount of discharge on a glass slide and roll the applicator back and forth across the slide as evenly as possible.
 - Allow the slide to air dry. Do not fix or stain the slide.
 - Label the slide with subject's initials and unique subject number, visit number, and date.
 - Place the slide in a microscope slide holder. Label the holder with the subject's initials and unique subject number, visit number, and the date.
 - Gram stains should be shipped the day of collection; unless otherwise specified for weekends and holidays.
- Papanicolaou smear: Obtain a Pap smear if subject is ≥ 21 years old and has not had one within the past 3 years. Pap smears may be sent to a local lab.

- Test for *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Trichomonas vaginalis* as specified in the central laboratory manual utilizing the collection and shipment supplies provided. Cultures should be shipped on the day of collection; unless otherwise specified for weekends and holidays.
- Culture for *Herpes simplex* (only if suspected) as specified in the central laboratory manual utilizing the collection and shipment supplies provided. Cultures should be shipped on the day of collection; unless otherwise specified for weekends and holidays.

9.1.6. Gram Stain Processing and Interpretation

Gram stains will be obtained, processed, and shipped by individual study sites as described above (Section 9.1.5.). They will then be stained and interpreted by a blinded microbiologist at a central laboratory. The method of interpretation is according to the Nugent scoring system.¹¹

For secondary endpoint evaluations, Gram stain scores will be categorized as: 0-3 = normal; 4-6 = intermediate, and 7-10 = BV.

9.1.7. Diagnosis for Infection Study Enrollment

Following baseline assessment, the examining clinician/investigator will determine if the subject meets the criteria for a diagnosis of BV, VVC, or Mixed Infection. The clinical diagnosis (i.e. all 4 Amsel criteria for BV diagnosis; combined symptom and sign severity score ≥ 2 and yeast on KOH wet mount for VVC diagnosis; and all 4 Amsel criteria, a combined symptom and sign severity score ≥ 2 , and yeast on KOH microscopy for Mixed Infection diagnosis) will determine if a subject qualifies for enrollment.

9.1.8. Randomization and Drug Dispensing

After determining that a subject meets all entry criteria, the investigator/designee will obtain a subject and a Drug Kit number via the IVR/IWR system. The Drug Kit corresponding to the assigned subject number will be dispensed to the subject.

At the time of dispensing, the subject's initials and number will be entered on both parts of the two-part tear-off label attached to the Drug Kit. The tear-off portion of the label will then be affixed to the appropriate page of the subject's CRF. (The other portion will remain on the Drug Kit box being dispensed.) This will allow Curatek to verify that the correct Drug Kit was dispensed to the correct subject by matching the Drug Kit number on the label in the subject's CRF to the Drug Kit number assigned to the subject via the IVR/IWR system. A hard copy of the IVR/IWR system's confirmation of the Drug Kit number assigned to the subject should be maintained with the subject's source documents.

9.1.9. Subject Instructions

At randomization, subjects will be dispensed their assigned Drug Kit which contains study drug along with instructions for the administration/use of the drug, study instructions, and a subject diary to track drug dosing and study compliance, symptom resolution/reoccurrence, and adverse events, should any occur. Subjects will record diary data between Visits 1 and 2.

The following study instructions will be reviewed with all subjects at Visit 1.

- Instruct the subject on proper dosing of study drug.
- Demonstrate how to open the drug tube, fill the applicator, and administer the drug. Sample tubes and applicators will be available for this purpose.

- Remind the subject to begin study drug within 2 days of the baseline visit (Visit 1).
- Counsel the subjects of child bearing potential on the requirement to continue an acceptable method of birth control while in the study.
- Counsel the subject not to engage in sexual intercourse through Visit 2 and to use provided non-lubricated condoms within the preceding 48 hours of Visit 3 if sexual intercourse occurs.
- Remind the subject not to use intravaginal/vulvovaginal products (e.g. feminine hygiene products such as douches and deodorants; contraceptive products such as diaphragms, spermicidal creams, gels, and foams; vaginal lubricant, moisturizers and hormonal suppositories and creams such as Vagifem®, Estrace® and Premarin® cream; and tampons) through Visit 2 and within 48 hours of Visit 3. Subjects should also be encouraged not to use these products at any time during study enrollment.
- Instruct the subject to abstain from alcohol and propylene glycol ingestion during study treatment and for 1 day thereafter.
- Review prohibited medications with subject: systemic and intravaginal/vulvovaginal antifungal, antimicrobial (other than study drug), and corticosteroid drugs (inhaled, intranasal, intra-articular, and/or topical steroids [provided they are not intravaginal/vulvovaginal] are not prohibited); and immunosuppressants.
- Counsel the subject to inform the investigator/study staff if there are any changes to concomitant medications or if new medications are taken.
- Show example subject diary and explain how to complete it properly. Instruct the subject to return it at the next visit.
- Remind the subject that unused drug must be placed inside the return packaging provided, sealed, and returned at the next visit.
- Instruct the subject to contact the office/clinic if she is concerned about any adverse events during treatment or if her symptoms remain bothersome.

A date and time should be scheduled for Visits 2 and 3.

9.2. Test of Cure Visit (Visit 2)

The procedures listed below will be performed 7-14 days after randomization for the purpose of determining subject compliance/evaluability with drug administration and study instructions, evaluating the subject's response to therapy and whether or not additional treatment is needed (i.e. cure or failure), and obtaining information on concomitant medication use and possible adverse events. If the subject is menstruating on the day of this scheduled follow-up visit, she should be rescheduled to return 24 hours after completion of menses.

9.2.1. Review of Diary

The diary should be reviewed with the subject and any discrepancies noted between the diary and subject report during the visit should be addressed. Reconciliation of discrepant information should be made and documented in the subject's source notes. If the subject diary is not returned at Visit 2, the subject should be reminded to return it at the next visit. Reasonable attempts to retrieve a diary if it is not returned at scheduled visits should be made and documented in the subject's source notes.

9.2.2. Inquire Regarding Compliance

Subjects should be asked the questions listed below to determine compliance with study drug administration and study instructions.

1. Did you start your study medicine more than two days after your office/clinic visit?

2. Were there any problems with taking your study medicine as prescribed; that is one applicatorful of medicine at bedtime for three days in a row?
3. On which days did you take your study medicine?
4. Did you have menstrual bleeding during treatment?
5. Have you taken/received any systemic (oral, IM, or IV) or intravaginal/vulvovaginal antifungal, antimicrobial (other than study drug), corticosteroid, or immunosuppressant drugs since starting the study?
6. Have you used any intravaginal/vulvovaginal products (other than study drug) since starting the study?
7. Did you have sexual intercourse since starting the study?

If the subject answers “Yes” to questions 1, 2, 4, 5, 6, or 7 or if the subject’s response to question 3 does not indicate that study drug was taken for three consecutive days, a protocol violation occurred. Protocol violations should be documented in subject’s source documents, the CRF, and reported to Curatek and to the IRB as per reporting guidelines.

Subjects with the above protocol violations may remain in the study and be evaluated at Visit 3 and have all per protocol procedures performed. One exception is subjects who used prohibited systemic, intravaginal/vulvovaginal antifungal, antimicrobial, and/or corticosteroids for the treatment of vaginal discomfort/symptoms. These subjects should be terminated from the study at Visit 2.

9.2.3. Time to Symptom Resolution/Reoccurrence

Symptom resolution and reoccurrence will be assessed by review of the subject’s diary and subject interview. Dates of symptom resolution and/or symptom recurrence should be documented.

9.2.4. Subject Assessment of Symptoms

Subjects will be asked to rate their current vulvovaginal symptoms of itching, burning, and irritation as absent=0, mild=1, moderate=2, or severe=3. The sum of this symptom score will be added to the vulvovaginal signs score obtained during the pelvic examination to determine a combined symptom and sign severity score.

9.2.5. Laboratory Tests and Specimen Collections

The lab tests listed below will be obtained at Visit 2.

- CBC with differential and blood chemistries (i.e. BUN, Creatinine, ALT, AST, ALP, and bilirubin) only for subjects enrolled in the Mixed Infection Study
- Vaginal culture for *Candida* species
- Vaginal Gram stain

9.2.6. Pelvic Examination and Specimen Collections

A non-lubricated speculum (tap water rinse acceptable) should be used during the pelvic examination. Components of the pelvic examination should be performed as described above in Section 9.1.5 (Pelvic Examination and Specimen Collections) and include the following:

- Vulvovaginal signs rating
- Vaginal discharge characterization
- Vaginal pH measurement

- Whiff test and saline wet mounts^h
- Vaginal *Candida* culture
- Vaginal Gram stain

9.2.7. Inquire Regarding Adverse Events

Subjects should be asked whether or not they experienced any adverse events since starting study drug. If so, information regarding the adverse event(s) should be obtained.

9.2.8. Inquire Regarding Changes in Concomitant Medication

Subjects should be asked if there have been any changes to medications that were being taken at the start of the study and/or new medications taken since the start of the study.

9.2.9. Collection of Unused Study Drug

Study staff should collect unused study drug from subjects for subsequent return to Curatek/designee.

9.2.10. Assessment of Clinical Status: Need for Additional Treatment

Following subject evaluation, the investigator/clinician will be asked to document whether the subject requires any additional treatment for vaginal discomfort/symptoms. Subjects who do require additional treatment should be treated per investigator/clinician judgment and terminated from the study. These subjects should have all visit 2 procedures completed (see Appendix A, Schedule of Procedures). Subjects who do not require treatment (and subjects who did not self-medicate) may remain in the study and return for their regularly scheduled follow up visit (Visit 3).

9.2.11. Determination of Cure or Failure of Subject's Enrolled Infection

BV subjects will be evaluated for BV cure. All three of the clinical criteria listed below must be satisfied in order to be considered a BV cure (i.e. clinical cure).

- Discharge has returned to normal/physiologicⁱ
- The whiff test is negative for any amine “fishy” odor.
- The saline wet mount is < 20% clue cells.

If in the investigator/clinician's opinion the subject requires additional treatment for BV or if the subject self-administered drug therapy for vaginal discomfort/symptoms after completing therapy, the subject will be considered a BV failure.^j

VVC subjects will be evaluated for VVC cure. In order to be considered a VVC cure, all signs and symptoms attributable to VVC must be resolved (i.e. clinical cure).

If in the investigator/clinician's opinion the subject requires additional treatment for VVC or if the subject self-administered drug therapy for vaginal discomfort/symptoms after completing therapy, the subject will be considered a VVC failure.^j

^h Subjects found to have motile trichomonads on saline wet mount at Visit 2 should be treated per investigator judgment and terminated from the study. These subjects should have all visit 2 procedures completed, per protocol. They will not be evaluable for the PP analysis.

ⁱ In the event a subject treated for BV gets a secondary yeast infection following treatment and discharge is consistent with VVC (i.e. white, creamy, and curdy [cottage cheese like] adherent to the epithelium), the subject will be considered a clinical cure providing all other clinical criteria for BV cure are met and the subject has a positive yeast culture.

^j Self-administration of therapy includes prescription and OTC antimicrobial, anti-fungal, analgesics, or steroid treatments.

Mixed Infection subjects will be evaluated for Mixed Infection cure.

- A Mixed Infection cure is a subject who meets the definition of a BV cure AND a VVC cure.

If in the investigator/clinician's opinion the subject requires additional treatment for either BV, VVC, or Mixed Infection or if the subject self-administered drug therapy for vaginal discomfort/symptoms after completing therapy, the subject will be considered a Mixed Infection failure.^k

9.2.12. Subject Instructions

The instructions listed below should be reviewed with all subjects continuing in the study:

- Counsel the subject on the requirement to continue an acceptable method of birth control while in the study (i.e. if of child bearing potential and sexually active with men who have not been sterilized).
- Remind the subject to have their partner use a non-lubricated condom if sexual intercourse occurs within the preceding 48 hours of Visit 3.
- Remind the subject not to use any intravaginal/vulvovaginal products within 48 hours of Visit 3. Subjects should also be encouraged not to use these products at any time during study enrollment.
- Review prohibited medications with subject: systemic and intravaginal/vulvovaginal antifungal, antimicrobial (other than study drug), and corticosteroid drugs (inhaled, intranasal, intra-articular, and/or topical steroids [provided they are not intravaginal/vulvovaginal] are not prohibited); and immunosuppressants.
- Counsel the subject to inform the investigator/study staff if there are any changes to concomitant medications or if new medications are taken.
- Instruct the subject to contact the office/clinic if she is concerned about any adverse events during treatment or if her symptoms remain bothersome.

Remind the subject of the date and time of her Visit 3 appointment. If an appointment has not been set, schedule one (i.e. 21-30 days after randomization).

If the subject did not return her diary or unused medication at Visit 2 remind her to bring the missing items to Visit 3.

9.3. Follow Up Visit (Visit 3)

The following procedures will be performed 21-30 days after randomization for the purpose of determining subject compliance; determining either presence or absence of the subject's baseline infection and whether or not additional treatment is needed; and obtaining information on concomitant medication use and possible adverse events.

If a subject was unable to return for Visit 2 but returns for Visit 3, available information that was to be obtained at Visit 2 regarding study drug administration/compliance and time to resolution/reoccurrence of symptoms may be obtained at Visit 3. The subject's diary should be reviewed and unused drug collected. Subjects in the Mixed Infection Study who missed Visit 2 should have hematology and chemistry labs obtained.

^k Self-administration of therapy includes prescription and OTC antimicrobial, anti-fungal, analgesics, or steroid treatments.

9.3.1. Inquire Regarding Compliance

Subjects should be asked the following questions to determine protocol compliance.

1. Have you taken/received any systemic (oral, IM, or IV) or intravaginal/vulvovaginal antifungal, antimicrobial (other than study drug), corticosteroid, or immunosuppressant drugs since starting the study?
2. Have you used any intravaginal/vulvovaginal products (other than study drug) prior to Visit 2 or within 48 hours of Visit 3?
3. Have you had sexual intercourse prior to Visit 2 or sexual intercourse without using a non-lubricated condom within 48 hours of Visit 3?

If the subject answers “Yes” to questions 1, 2, or 3 above, a protocol violation occurred. Protocol violations should be documented in subject’s source notes, the CRF, and reported to Curatek and to the IRB as per reporting guidelines. All Visit 3 procedures should be performed on these subjects.

9.3.2. Subject Assessment of Symptoms

Subjects will be asked to rate their current vulvovaginal symptoms of itching, burning, and irritation as absent=0, mild=1, moderate=2, or severe=3. The sum of this symptom score will be added to the vulvovaginal signs score obtained during the pelvic examination to determine a combined symptom and sign severity score.

9.3.3. Laboratory Tests and Specimen Collections

The lab tests listed below will be obtained at Visit 3.

- Vaginal culture for *Candida* species
- Vaginal Gram stain

9.3.4. Pelvic Examination and Specimen Collections

A non-lubricated speculum (tap water rinse acceptable) should be used during the pelvic examination. Components of the pelvic examination should be performed as described above in Section 9.1.5 above (Pelvic Examination and Specimen Collections) and include the following:

- Vulvovaginal signs rating
- Vaginal discharge characterization
- Vaginal pH measurement
- Whiff test and saline wet mounts¹
- Vaginal *Candida* culture
- Vaginal Gram stain

9.3.5. Inquire Regarding Adverse Events

Subjects should be asked whether or not they experienced any adverse events since starting study drug. If so, information regarding the adverse event(s) should be obtained.

9.3.6. Inquire Regarding Changes in Concomitant Medication

Subjects should be asked if there have been any changes to medications that were being taken at the start of the study and/or new medications taken since the start of the study.

¹ Subjects found to have motile trichomonads on saline wet mount at Visit 3 should have all Visit 3 procedures completed. Subjects should be treated per investigator/clinician judgment. They will not be evaluable for the PP analysis.

9.3.7. Assessment of Clinical Status: Need for Additional Treatment

Following subject evaluation, the investigator/clinician will be asked to document whether the subject requires any additional treatment for vaginal infection. Subjects who do require additional treatment should be treated per investigator/clinician judgment.

9.3.8. Distribution of Subject Satisfaction Survey

Subjects should be given the Subject Satisfaction Survey and asked to complete the form before leaving the clinic (Appendix E). Completion of the survey is voluntary and does not affect participation in the study in any way.

9.4 Unscheduled Visits

Unscheduled visits are visits that occur less than 7 days after randomization or between Visit 2 and Visit 3. If the subject or investigator has concerns about persistent symptoms or adverse events that require an unscheduled visit, the subject may return to the office/clinic to be evaluated. If the subject needs additional treatment for vaginal discomfort/symptoms (either based on investigator judgment or as a result of the subject self-medicating) before Visit 2, then Visit 2 procedures should be completed. If such an unscheduled visit occurs between Visit 2 and Visit 3 then Visit 3 procedures should be completed. If the subject does not need to be treated, and is willing, she may remain in the study and return for her next scheduled visit.

In instances where Visit 1 lab results make a subject ineligible for the study (i.e. subject randomized but did not meet inclusion/exclusion criteria), subjects should be terminated when exclusionary lab results become known. Procedures for these subjects are more limited but require a safety assessment including collection of adverse events, concomitant medications, and safety blood labs if the subject was enrolled in the Mixed Infection Study and safety labs were not already obtained at Visit 2. Subject diaries should be reviewed and unused drug tubes collected. Drug administration/compliance should be ascertained if not already done. Lab results that would make a subject ineligible are: positive gonorrhea, chlamydia, trichomonas, or herpes tests; normal Nugent score < 4 (for BV and Mixed Infection subjects); or negative *Candida* culture (for VVC and Mixed Infection subjects). See Appendix A, Schedule of Procedures.

Other reasons for an unscheduled visit include withdrawal by subject or investigator decision, or pregnancy (see Section 10.1).

10. Adverse Events and Safety Reporting

All adverse events occurring during the course of the clinical study, regardless of relation to study drug, will be recorded in source documentation and on the appropriate page(s) of the CRF. The investigator will assess subjects for the occurrence of adverse events at both follow-up visits. Subject diaries will also be reviewed for the occurrence of adverse events. Spontaneously reported adverse events by subjects at any time during the study will also be recorded.

10.1. Definition of Adverse Event/Adverse Reaction/Suspected Adverse Reaction

An adverse event (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use

of a drug, without any judgment about causality. An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

Pre-existing conditions are not considered adverse events unless there is an unexpected change in the frequency, intensity, or nature of the condition. Pre-planned hospitalizations, diagnostic or elective procedures/surgeries for pre-existing conditions, where there is no change in the subject's condition, will not be considered adverse events.

A newly diagnosed pregnancy during study enrollment will also not be considered an adverse event. If a pregnancy occurs during the dosing phase of the study, the subject will be asked to discontinue study drug and be terminated from the study. Curatek/Curatek's designee should be notified via phone, fax, or e-mail/scan within 24 hours of the site learning of the pregnancy. A pregnancy notification form must be completed and sent to Curatek/Curatek's designee. Subjects should be asked to provide consent on an authorization for disclosure of medical information form so that follow-up information regarding the pregnancy outcome could subsequently be obtained. If a pregnancy results in an abnormal outcome (i.e. a congenital anomaly/birth defect, neonatal death, stillbirth, spontaneous abortion etc.) a serious adverse event must be reported.

10.2. Protocol-Specific Adverse Event Considerations

For purposes of this study, spontaneous reports of vaginal discharge and/or vulvovaginal signs and symptoms (e.g. itching, burning, irritation, erythema etc.) associated with the application of study drug should be reported as adverse events. However, changes in clinical criteria (i.e. Amsel criteria and/or vulvovaginal signs and symptoms) from baseline that are associated with one of the vaginal infections under study (i.e. BV, VVC, or Mixed Infection) will be captured on the corresponding CRF page and should not be recorded as adverse events with the following exceptions:

- If in the investigator/clinician's opinion a subject treated for BV gets a secondary yeast infection, the yeast infection should be captured as an adverse event.
- If in the investigator/clinician's opinion a subject treated for VVC gets BV, the BV should be captured as an adverse event.

10.3. Definition of Serious Adverse Events (SAE)

Each adverse event or suspected adverse reaction must be assessed for its seriousness. The term "serious" is not synonymous with "severe" that may be used to describe the intensity of an event or reaction. An AE or suspected adverse reaction is considered serious if in the view of either the investigator or sponsor:

- Results in death
- Is life threatening
The term "life threatening" refers to an adverse event or suspected adverse reaction in which either the investigator or the sponsor believe the subject was at risk of death at the time of the event or reaction; it does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongs an existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is considered medically important

Important medical events are those that may not be immediately life threatening, but are of major clinical significance and may require intervention to prevent one of the other serious outcomes listed above. Examples include a seizure that did not require in-subject hospitalization or allergic bronchospasm that necessitated emergency treatment.

All adverse events or suspected adverse reactions that do not meet the criteria for serious will be regarded as non-serious.

10.4. Definition of Unexpectedness

An adverse event or suspected adverse reaction is considered unexpected if the nature/specificity or severity of the event or reaction is not consistent with applicable product information (e.g. Investigator's Brochure for an unapproved investigational product or a package insert/summary of an approved product).

The current Investigator's Brochure lists the adverse events or suspected adverse reactions known to be associated with metronidazole and terconazole.

10.5. Documentation of Adverse Events

All adverse events (i.e. serious and non-serious) that occur from the time informed consent is signed through Visit 3 must be reported and recorded in source documentation and on the appropriate page(s) of the CRF. Information to be documented for each adverse event includes the following: adverse event term, severity of the event (i.e. mild, moderate or severe), start and stop date (if applicable) of the event, time of event if event occurred on the first day of study drug administration, relationship to study drug (i.e. none, possible, probable, definite), action taken with the study drug (i.e. none, study drug interrupted, study drug discontinued), action taken for the adverse event (i.e. none, new medication/treatment, terminated, hospitalized, or other), outcome of the event (resolved, resolved with sequelae, ongoing, death, or unknown) and whether or not the event meets serious criteria.

If adverse event signs and symptoms are the result of a specific diagnosis, the diagnosis only (and not the cluster of signs and symptoms that make up the diagnosis) should be reported on the CRF.

10.6. Severity Criteria

Severity criteria for adverse events will be defined as follows:

- Mild: awareness of signs/symptoms that are easily tolerated causing minimal discomfort and not interfering with normal daily activities
- Moderate: Sufficient discomfort is present and may interfere with normal daily activities
- Severe: Extreme distress is present causing significant impairment of functioning or incapacitation preventing normal daily activities

The investigator should use clinical judgment in assessing the intensity of adverse events not directly experienced by the subject (e.g. lab abnormalities).

10.7. Relatedness Criteria

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or definite. Attribution definitions for the relatedness of adverse events will be defined as follows:

- None: An adverse event that is not related to the use of study drug

- Possible: An adverse event that might be due to the use of the drug; an alternative explanation (e.g. a concomitant drug or illness) is inconclusive. The relationship to time is reasonable.
- Probable: An adverse event that might be due to the use of the drug; an alternate explanation (e.g. a concomitant drug or illness) is less likely. The relationship in time is suggestive.
- Definite: An adverse event that cannot be reasonably explained with an alternate explanation (e.g. a concomitant drug or illness). The relationship in time is very suggestive. A direct cause and effect relationship between the study drug and the adverse event exists.

10.8. Serious Adverse Event Reporting

All serious adverse events (SAE) that occur during the trial regardless of their relationship to study drug must be reported to Curatek/Curatek's designee as soon as possible but no later than 24 hours after learning of the event. Initial notification may be made via phone, fax, or e-mail/scan.

Additionally, a Serious Adverse Event (SAE) Report form must be filled out and sent via fax or e-mail/scan to Curatek/Curatek's designee as soon as possible. Information included with initial notification should include as much of the information requested on the form as possible. The SAE Report form should not be held up if all the information regarding the SAE is not yet available. The Concomitant Medications and the Adverse Events CRF pages should also be faxed or e-mailed/scanned with the SAE Report form.

When additional/new information regarding the SAE becomes available, an updated SAE Report form, Concomitant Medications, and Adverse Events CRF pages should be promptly submitted to Curatek/Curatek's designee. Copies of any relevant data from hospital notes (e.g. laboratory tests, discharge summary, ECGs, ER records etc.) should also be submitted when they become available.

Specific contact information for the reporting of SAEs and submission of the SAE Report form and accompanying documents will be available on the Serious Adverse Event (SAE) Report form and on the contact list for the study.

All serious adverse events should be followed and treated appropriately until there is satisfactory resolution of the adverse event, the adverse event becomes stable or can be explained by other causes, clinical judgment indicates further evaluation is not needed, or it appears unlikely that additional information can be obtained given due diligence has been done.

Investigators must comply with all applicable regulatory requirements related to the reporting of serious adverse events (i.e. regulatory authorities, IRB, institution reporting requirements etc.).

10.9. Safety Reporting to Investigators, IRBs, and Regulatory Authorities by Curatek

Curatek/Curatek designee will be responsible for reporting to the regulatory authorities (i.e. FDA) and all participating investigators any adverse event associated with the use of study drug (i.e. suspected adverse reaction) that is both serious and unexpected; or any findings from clinical, epidemiological, or pooled analysis from multiple studies or any findings from animal or in vitro testing that suggest a significant risk in humans exposed to the drug in an IND safety report. IND safety reports will be sent as soon as possible but in no event later than 15 calendar days after Curatek/Curatek's designee's initial receipt of the information.

Curatek/Curatek's designee will also notify the FDA by telephone or fax of any unexpected fatal or life-threatening experience associated with the use of the study drug (i.e. suspected adverse reactions) as soon as possible but in no event later than 7 calendar days after Curatek/Curatek's designee's initial receipt of the information.

Follow-up information to a safety report (if applicable) will be submitted as soon as relevant information is available.

Study sites utilizing a local IRB must report IND safety reports to their reviewing IRB and institution in accordance with IRB regulations and institutional policies. Curatek/Curatek's designee will report IND safety reports to the reviewing central IRB on behalf of those sites utilizing a central IRB.

Curatek/Curatek's designee will be responsible for safety oversight, which includes the review of all adverse events. If there are concerns on the part of any investigator or Curatek that would prevent the study from continuing, the study will be terminated at that time and no more subjects will be enrolled.

11. Statistical Methods

Summary statistics of all important demographic, study conduct, efficacy, and safety data will be provided in tables. Case report form, clinical laboratory, and efficacy evaluation data will be provided in listings.

11.1. General Methods

Data from this study will be summarized with descriptive statistics. Descriptive summaries of baseline and demographic data will include frequency and percent relative frequency for categorical data; frequency and median for ordinal data; and frequency, mean, standard deviation, and minimum and maximum for quantitative data. In addition, 95% confidence intervals will be calculated, as appropriate.

For scheduled measurements which are repeated out of schedule, such as repeat laboratory tests, the last measurement within a scheduled time interval will be used for data summaries. All results, whether scheduled or repeat, will be listed.

Each of the three infection studies within the trial will be analyzed separately.

The primary statistical objective of each infection study is listed below:

1. BV Study: Demonstrate the superiority of BV Gel (0.9% metronidazole gel) to Placebo Gel in the treatment of bacterial vaginosis (BV).
2. VVC Study: Demonstrate the superiority of VVC Gel (0.8% terconazole gel) to Placebo Gel in the treatment of vulvovaginal candidiasis (VVC).
3. Mixed Infection Study: Demonstrate the superiority of Combo Gel (0.9% metronidazole gel and 0.8% terconazole gel) to both single entity gels (BV Gel alone and VVC Gel alone).

The primary and secondary endpoints are reflective of each of the infection studies within the protocol include:

- **Primary Endpoints**

- BV Study: BV cure rate defined as normal/physiologic discharge^m, negative whiff test, and < 20% clue cells (i.e. clinical cure)
 - VVC Study: VVC cure rate defined as resolution of all signs and symptoms attributable to VVC (i.e. clinical cure)
 - Mixed Infection Study: Mixed Infection cure rate defined as BV cure (i.e. BV clinical cure) **AND** a VVC cure (i.e. VVC clinical cure)
- **Secondary Endpoints**
 - BV Study: BV clinical and Gram stain Nugent score cure rates alone and combined; changes/improvements in Amsel criteria and Nugent scores; time to resolution of symptoms
 - VVC Study: VVC clinical (i.e. resolution of all signs and symptoms attributable to VVC) and mycologic cure rates (i.e. negative *Candida* on culture) alone and combined; changes/improvements in signs and symptoms scores; eradication (or persistence) of individual fungal species; time to resolution of symptoms
 - Mixed Infection Study: BV clinical and Gram stain Nugent score cure rates alone and combined; changes/improvements in Amsel criteria and Nugent scores; VVC clinical and mycologic cure rates alone and combined; changes/improvements in signs and symptoms scores; eradication or persistence of individual fungal species; time to resolution of symptoms

A Statistical Analysis Plan (SAP) will be prepared, with comprehensive details for all statistics to be presented for both primary and secondary endpoints of each study.

11.2. Study Conduct Summaries

The number of subjects who were enrolled, treated with at least one dose of study drug, who completed the study, as well as the reasons for withdrawal, will be summarized with counts and percentages by treatment group within each infection study and for the trial overall. This table will also include number of screening failures and reasons for screening failures. Protocol violations, inclusion/exclusion criteria, and study drug administration data will also be summarized.

11.3. Analysis Populations

The primary assessments of efficacy will be based on the modified intent-to-treat (mITT) population. In addition to the mITT analyses of the data, analyses will be conducted using the intent-to-treat (ITT) population as well as the per protocol (PP) population. The data analysis populations are defined as:

- ITT: The intent-to-treat analysis will include all subjects randomized to treatment.
- mITT: The modified intent-to-treat population will include all subjects randomized to treatment and administered at least one dose of study drug. In addition, subjects in the VVC and Mixed Infection studies must have a positive baseline vaginal fungal culture for *Candida* species. Subjects in the BV and Mixed Infection studies must have a Gram stain Nugent score of ≥ 4 at the baseline visit.
- PP: The per protocol analysis will include the subset of mITT subjects that had no major protocol violations and who are classified as efficacy evaluable with no missing data required to determine primary endpoints. Major protocol violations likely to bias assessment of the primary endpoint for the per protocol population will be determined prior to unblinding the data.

^m In the event a BV subject has discharge consistent with VVC (i.e. white, creamy, and curdy [cottage cheese like] adherent to the epithelium), the subject will be considered a BV cure providing all other criteria for BV cure (and evaluability) are met and the subject has a positive yeast culture.

- Safety: The safety population will include all subjects randomized to treatment and administered at least one dose of study drug.

11.4. Determination of Sample Size

Approved labeling, clinical data included in New Drug Applications and approval packages, and sponsor experience with the compounds in this study and similar therapies provide the following estimates and ranges of the cure rates (as proportions) for the treatments within each infection study.

1. BV Subjects
 - a. BV Gel (0.9% metronidazole gel): .50 (.35-.45)
 - b. Placebo Gel: .20 (.10-.20)
2. VVC Subjects
 - a. VVC Gel (0.8% terconazole gel): .70 (.65-.75)
 - b. Placebo Gel: .20 (.15-.25)
3. Mixed Infection Subjects
 - a. Combo Gel (0.9% metronidazole gel and 0.8% terconazole gel): .35 (.25-.35)
 - b. VVC Gel (0.8% terconazole gel): .10 (.05-.15)
 - c. BV Gel (0.9% metronidazole gel): .10 (.05-.15)

Under the assumption that the above estimated cure rates will be observed in this study, sample sizes were calculated for each infection study based on these estimates for at least 90% power and at least 50 subjects per treatment group. Superiority tests will be performed as two-sided, $\alpha = 0.05$ level significance tests, and sample sizes were calculated using Fisher's Exact test in case the planned Chi-squared test is not appropriate.

The following table provides the sample size required for each treatment group within each infection study. The total sample size is given, and represents the number of evaluable subjects required (Per Protocol population). Entry in each infection study of the trial will be stopped when this number of evaluable subjects is reached, since evaluable/not-evaluable can be determined from the completed case report form prior to unblinding.

Required Number of Evaluable Subjects, by Infection Study and Treatment Group							
<i>Study:</i>	<i>BV Only Subjects</i>		<i>VVC Only Subjects</i>		<i>Mixed Infection Only Subjects</i>		
Treatment Arm:	BV Gel	Placebo Gel	VVC Gel	Placebo Gel	BV Gel	VVC Gel	Combo Gel
Expected Cure Rate	50%	20%	70%	20%	10%	10%	35%
n for at least 80% Power, and at least 50 per group	58	58	50	50	63	63	63
Actual Power	90.0%		>99.9%		90%		
Total N	405						

Thus, subjects will be enrolled until approximately 405 evaluable subjects, as indicated above, for all three infection studies, have completed the trial.

11.5. Handling of Missing Data

By definition, all subjects in the PP population will have sufficient data required to determine primary endpoints. In instances where some of the data is missing, two situations are possible: 1) some data are not available but the data that is available indicates for certain the patient is a failure, and 2) the data that is available indicates a possible cure and nothing indicates a failure, but without complete data it is not possible to determine for certain it is indeed a cure. Thus, a patient with situation 1) will be considered evaluable, while a patient with situation 2) will be non-evaluable.

For subjects who are not eligible for inclusion in the PP populations but who are eligible for inclusion in the mITT and/or ITT subject populations, all missing data will be imputed as worst-case scenario outcome (e.g. failure).

11.6. Efficacy Analyses

11.6.1. Primary Efficacy Analysis

The primary efficacy endpoint is the cure rate at the test-of-cure visit (Visit 2). Definitions of cure for each of the three infection studies are provided in Section 11.1.

Subjects in all studies will be categorized as cure or failure for the ITT and mITT analyses, and as cure, failure or non-evaluable for the PP analysis. The number and percentage of subjects in each treatment group in each of these categories will be reported. Separate statistical analyses will be performed for each of the three infection studies. All treatment comparisons will be based on two-tailed 0.05 significance level hypothesis tests and 95% confidence intervals for the difference in proportion of successes in each treatment. The primary comparison of treatment groups for each study will be performed using a continuity corrected Chi-squared test. It is anticipated that in some treatment groups in one or more of the infection studies, there may not be sufficient expected cell counts for the Chi-squared test and confidence intervals based on the normal approximation to be accurate. Therefore, when this occurs, Fisher's Exact test and exact binomial confidence intervals will be constructed.

The primary efficacy analysis for each of the three infection studies will be performed using the mITT population with worst case scenario imputation for missing data. Supportive analyses will also be conducted using the PP population.

BV Study: The primary statistical objective of the BV infection study is to demonstrate the superiority of BV Gel to Placebo Gel in the treatment of BV. The assessment of superiority will be performed by conducting a continuity corrected Chi-squared test for a difference in the proportion of BV cure between the two treatments. Also, a 95% two-sided confidence interval for the difference in proportion of BV cure between the two treatments will be constructed.

VVC Study: The primary statistical objective of the VVC infection study is to demonstrate the superiority of VVC Gel to Placebo Gel. The assessment of superiority will be performed by conducting a continuity corrected Chi-squared test for a difference in the proportion of VVC cure between the two treatments. Also, a 95% two-sided confidence interval for the difference in proportion of VVC cure between the two treatments will be constructed.

Mixed Infection Study: The primary statistical objective of the Mixed Infection Study is to demonstrate the superiority of the Combo Gel to both BV Gel and VVC Gel. The assessment of superiority will be performed by conducting a continuity corrected Chi-squared tests for a difference in the proportion of Mixed Infection cure between the Combo Gel and each of the two single entity treatments. If the P-values for both of the hypothesis tests are less than or equal to 0.05, the Combo Gel will be considered superior to both of the single entity gels. Despite there being two comparisons made within the same study, no adjustment for multiplicity is necessary since both comparisons must be positive instead of “at least one,” in order to conclude superiority of the Combo Gel. Also, 95% two-sided confidence intervals for the difference in proportion of Mixed Infection cure between the Combo Gel and each of the two single entity treatments will be constructed.

11.6.2. Secondary Efficacy Analyses

Secondary efficacy endpoints are listed in Section 5.3. These endpoints include variables that are categorical (including binary variables), ordinal (such as rating scores), or time to event variables (such as time to resolution of symptoms). The analysis of the secondary endpoints will be performed using the mITT population with worst case scenario imputation for missing data, with supportive analyses conducted using the PP population.

For the secondary endpoints which are categorical or ordinal with four or fewer levels (including binary outcome variables), the analysis will include the proportion of subjects with each criteria or each score, at baseline and endstudy. The comparison of treatment groups will be performed using Chi-squared tests if all expected cell counts are at least 5, and Fisher’s Exact test otherwise. For binary outcomes, (clinical outcome, mycological outcome, and eradication [or persistence] of individual fungal species) 95% two-sided confidence intervals for the difference in proportions will also be constructed.

Secondary endpoints which are ordinal data with more than four levels, such as Nugent score, the median score at baseline, endstudy, and the change from baseline will be computed, in addition to the proportion of subjects at each level. Treatment comparisons will be performed using the Wilcoxon Rank Sum test.

The secondary endpoint of time to resolution of symptoms will be analyzed in each infection study using log-rank tests and Kaplan-Meier plots. Kaplan-Meier estimates of the quartiles for time to resolution will be computed, along with 95% confidence intervals.

The analysis of eradication (persistence) of individual fungal species will be conducted in subgroups of subjects defined by fungal species present at baseline (for the VVC and Mixed Infection studies).

11.7. Safety Analysis

Safety will be assessed through summaries of adverse events (AEs) and laboratory evaluations. All safety analyses will be based on the safety population, as defined in Section 10.3 and will be summarized for

each treatment group. These summaries will be presented separately for each infection study. In addition, adverse events, as available, for BV Gel and VVC Gel will also be summarized by combining subjects who received the same treatment regimen across the studies. For example, those receiving BV Gel in the BV study will be combined with those receiving BV Gel in the Mixed Infection Study.

11.7.1. Adverse Events

Adverse events will be coded by system organ class and preferred term using a current version of Medical Dictionary for Regulatory Activities (MedDRA). Each verbatim adverse event will be translated to a preferred term, a higher-level included term, and finally a system organ class. Adverse events will be summarized at each level of the hierarchy, counting proportions of the subjects who experienced at least one such adverse event. Frequencies of subjects with treatment-emergent adverse events (TEAEs), sorted by system organ class, will be summarized by treatment group. TEAEs are defined as those AEs that develop or worsen after the first dose of study drug and up to the date of the final visit. Any adverse events that are not considered treatment emergent will be provided in listings.

A secondary analysis of TEAEs judged by the investigator to be related to study drug will be performed. This analysis will be summarized identically to the above analysis. Additional breakdowns of serious adverse events (SAEs) and treatment-related SAEs will be summarized and described in a similar fashion.

Summaries of AE durations, severity, relatedness to study drug, countermeasures taken, outcome, and seriousness will also be produced as warranted. At the least, incidence of study drug discontinuation and death will be summarized.

11.7.2. Laboratory Assessments

CBC with differential and blood chemistry data will be tabulated and compared to baseline for the Mixed Infection study population. Laboratory endpoints will be summarized for baseline, endstudy, and for change from baseline to endstudy using descriptive statistics (mean, median, standard error, minimum, and maximum). In addition, summarization of laboratory values that deviate substantially from the normal reference range will be provided. The reference ranges for normal laboratory values will be provided by the central laboratory.

Shift tables will be provided, which tabulate the proportion of subjects in each treatment group who change from low abnormal (< LLN), normal, or high abnormal (> ULN) at baseline to low abnormal, normal, or high abnormal at Visit 2, as shown in the following table.

	Baseline Lab Value:	Visit 2/EndStudy		
		< LLN	Normal	> ULN
Active Medication	< LLN	x (x.x%)	x (x.x%)	x (x.x%)
	Normal	x (x.x%)	x (x.x%)	x (x.x%)
	> ULN	x (x.x%)	x (x.x%)	x (x.x%)
Placebo	< LLN	x (x.x%)	x (x.x%)	x (x.x%)
	Normal	x (x.x%)	x (x.x%)	x (x.x%)
	> ULN	x (x.x%)	x (x.x%)	x (x.x%)

All laboratory data will be provided in listings. Abnormal laboratory values, defined as observations outside the normal range, will be flagged in the listing.

11.7.3. Vital Signs

Vital signs are only collected before administration of study drug, and will be summarized within each infection study pooling treatment groups. Vital sign data will also be presented in listings.

11.7.4. Physical Exams

All physical exam data will be presented in listings.

12. Data Handling and Record Keeping

12.1. Source Documents

Source data is all information in a clinical trial that would allow for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source documents are original documents and include: clinic, office, and hospital records (i.e. paper or electronic); source document worksheets that will be provided by Curatek to assist sites in capturing protocol required data; laboratory results; subject diaries; drug accountability records, etc. The nature and location of all source documents should be known to Curatek/Curatek's designee (and the study staff) so that original subject data recorded can be verified against data entered on the CRF. All source notes should be signed and dated by the investigator/study staff so that the author of the note/entry (and the date) can be identified.

12.2. Case Report Forms

Paper case reports forms (CRF) will be provided by Curatek Pharmaceuticals, LLC. Curatek/Curatek's designee will train appropriate study staff on the use of the CRFs. CRFs will be printed in triplicate on non-carbon required (NCR) paper. The original and one copy of each page of the CRF will be collected by Curatek/Curatek's designee during routine monitoring visits.

Case report forms should be completed in accordance with CRF completion guidelines provided by Curatek. All CRF entries and corrections must be made by the investigator or designee listed on a delegation of responsibility log. Corrections of data entered on the CRF must be made in the following manner:

- If the original CRF page is still at the study site, the incorrect entry will be crossed out (on the original page) with a single line so as to remain legible. No correction fluid or erasers are permitted. The correct data will then be entered in ink next to the crossed-out entry. Each correction, change, or addition of new data must be initialed and dated by the individual making the correction, change, or addition.
- If the original page has already been sent to Curatek/data management and a data error is noted by the site or the site monitor, a site initiated data clarification form (SIDCF) should be generated by the site or the site monitor and submitted to data management to request a data change. If data management believes a data point needs to be corrected/clarified, a data clarification form (DCF) will be generated by data management (either manually or automated) and sent to the site. In either instance, the original SIDCF or DCF will be retained by the site and a copy scanned to data management.

The investigator must initial or sign and date where indicated on the CRF page(s), indicating that all data entries are accurate and complete. The investigator must retain full responsibility for the accuracy and authenticity of all data entered on the CRFs from his/her site.

CRFs should be completed promptly after a subject visit unless data is pending regarding a lab or culture result or adverse event follow-up information. Data reported in the CRFs should be recorded/transcribed from source documents. Diaries filled out by subjects will be recognized as source documents.

The clinical monitor will review the CRF against appropriate source documents and evaluate all data entries for accuracy and completeness. If data is missing or errors are noted, the investigator/designee should correct the CRF as above.

12.3. Record Retention

U.S. FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after the last marketing application approval 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. All state and local laws for retention of records also apply.

These documents should be retained for a longer period of time if required by applicable regulatory requirements or by an agreement with Curatek. No documents should be destroyed unless written approval to do so has been received by Curatek. Written notification should be provided to Curatek for transfer of any records to another party or moving them to another location.

12.4. Data Management

The data management center will be determined by Curatek prior to the start of the study. Data will arrive by paper case report forms, except laboratory data which will arrive electronically from the central lab.

The data management center will use validated software to process both the paper case report forms and electronic laboratory data. An electronic audit trail will be maintained to document all changes to the database after double data entry or receipt of electronic data. Prior to processing data, a data management plan will be written by the data management center detailing the process steps involved and quality checks incorporated into the study. This document will be reviewed and approved by the sponsor, and updated during the study as needed.

13. Study Management

13.1. Monitoring and Source Data

Clinical monitors/representatives of Curatek Pharmaceuticals, LLC will perform on-site monitoring visits as often as necessary to ensure that all aspects of the protocol are followed. Monitors will record their visits on a site visit log that will be kept at the site. A site initiation visit (SIV) for the purpose of training the investigator(s) and study staff on the protocol, CRFs, and all related study activities will be conducted at each site prior to subject screening. The first post-initiation visit will take place shortly after subject enrollment begins at each site and a close out visit will occur after the last subject completes the study.

During monitoring visits, source documentation will be reviewed for verification of data entered on the CRF. Source documents include but are not limited to clinic and office charts (i.e. paper and/or

electronic), laboratory and vaginal culture results, Gram stain results, and subject diaries. In collaboration with Curatek, the study monitor will assist in assessing whether electronic records generated from computerized medical record systems used at investigational sites can serve as source documents for the purposes of this protocol. If a site's computerized medical record system is not adequately validated for the purposes of clinical research (as opposed to general clinical practice), applicable hardcopy source documents must be maintained to ensure that critical protocol data entered into the CRFs can be verified.

The review of regulatory documents, informed consents, and drug storage and accountability records will also be done during monitoring visits. Monitors will meet with the principal investigator periodically throughout the study to provide feedback on the study and the site's performance. Monitors will also provide feedback to Curatek regarding site visits on a regular basis.

Direct access to source documentation (i.e. paper and/or electronic), and to the drug storage and dispensing area must be allowed during monitoring visits. It is also expected that investigator/study staff will be available to assist the monitor in his/her activities, CRFs will be completed, and ICFs, drug accountability and regulatory records will be available for review. A suitable area should be provided for the monitor to work during monitoring visits.

13.2. Protocol Adherence

The investigator must read this protocol thoroughly and not deviate from it, unless a protocol waiver is received or it is necessary to eliminate an immediate hazard to study subjects. Should this occur the investigator should notify Curatek/Curatek's designee immediately and the reviewing IRB.

13.3. Protocol Amendments

Changes in any portion of this protocol after signatures of agreement are obtained must be presented in the form of an amendment, signed by Curatek and the principal investigator, and approved by the reviewing IRB prior to the amendment being implemented. The only time a protocol amendment may be initiated without IRB approval is when the change is necessary to eliminate apparent immediate hazard(s) to the subject(s). In such an event Curatek will forward the protocol amendment to the FDA and the investigator will forward it to the reviewing IRB. Minor study management issues, administrative changes, and typographical errors do not require protocol amendments.

13.4. Protocol Violations

All protocol violations should be documented in subject's source notes and on the appropriate CRF page. Protocol violations should be reported to Curatek and the reviewing IRB, as per their requirements.

13.5. Quality Assurance and Regulatory Agency Audits

The study site may be audited by the IRB, Curatek/Curatek designees, independent auditors, or regulatory agencies (i.e. FDA). If the site is contacted by a regulatory agency for an inspection, Curatek should be notified immediately.

In accordance with ICH guidelines, the investigator/institution must allow direct access to all trial related records for the reviewing IRB, Curatek/Curatek designees, auditors, and regulatory agencies (i.e. FDA).

14. Ethical and Regulatory Considerations

14.1. Ethical Considerations

All aspects of this study will be conducted in compliance with the protocol and in accordance with all applicable regulatory requirements, and in accordance with Good Clinical Practice (GCP). Investigators must also conduct the study in accordance with all of the above and any local/regional regulatory requirements. Many of the investigator responsibilities for this study are contained within the Form FDA 1572-Statement of Investigator which must be completed and signed before the investigator may participate in the study.

14.2. Institutional Review Board

This protocol (and any subsequent amendments) must be reviewed and approved by an appropriate Institutional Review Board (IRB) that complies with federal regulations 21CFR, Part 56 prior to initiation of the study. Curatek will supply all documents required for submission to the IRB for review and approval. These documents include the protocol, investigator's brochure, informed consent template, subject recruitment/advertising materials, written information that will be provided to subjects (i.e. instructions for subjects, instructions for using study drug, subject diary, and subject satisfaction survey) and any other documents that the IRB needs to fulfill its responsibilities. Formal written notification of the protocol and informed consent approval is required by Curatek prior to the study commencing and drug being shipped to the investigator. Approval letters must be dated and clearly identify the documents approved.

Investigative sites must adhere to all requirements stipulated by their reviewing IRB. These include notification to the IRB regarding protocol amendments, updates/changes to informed consents, protocol violations, recruitment/advertising materials, safety reporting requirements, ongoing review of the study at specified intervals, and submission of a final report. A copy of IRB approvals and relevant correspondence/documentation between the investigative site and the IRB must be maintained and provided to Curatek/Curatek's designee as requested.

Payment to subjects must be approved by the IRB and should not be so large as to present problems of coercion or exert undue influence for study participation.

14.3. Informed Consent

The investigator/designee will be responsible for obtaining written informed consent from each subject prior to performing any study-related procedures. (Assent for children between 12 and 18 years will be obtained per IRB requirements.) The consent form should be reviewed by Curatek/Curatek's designee (i.e. if changes were made from the informed consent template provided by Curatek) and must be approved by the reviewing IRB. The consent form should be in accordance with all applicable regulatory requirements, and in accordance with Good Clinical Practice (GCP).

Subjects should be given ample time to review the consent and ask any questions they may have. Once they decide to participate in the study, the informed consent must be signed and dated by the subject and by the person who conducted the informed consent discussion. The investigator/designee must document the informed consent process in the subject's source document. A copy of the signed informed consent should be given to the subject.

A written subject authorization (i.e. HIPAA authorization) either provided as a separate document or contained within the informed consent that explains to the subject the permissible uses and disclosures of

the subject's personal health information (PHI) must also be obtained. Stand-alone authorizations do not require review or approval from an IRB; however core elements and statements must be included in them.

If there are any revisions to the informed consent or to written materials given to the subjects, they should be IRB approved prior to their use. Subjects should be informed in a timely manner of any new information that becomes available during the course of the study that may be relevant to the subject's participation in the study. All revised informed consent forms must be reviewed and signed by the subject in the same manner as the original informed consent. The subject should receive a copy of the signed, revised consent and the date of re-consenting should be documented in the subject's source document.

All original signed and dated consent forms will be kept by the investigator.

14.4. Delegation Log

The investigator will maintain a delegation log throughout the study. The delegation log will comprise a listing of appropriately qualified persons to whom the investigator has delegated significant trial-related activities/tasks. The investigator should initial and date the delegation log at the beginning of the trial when activities/tasks are delegated and when changes occur. The investigator should also sign the delegation log at the end of the study; the completed log will be maintained in the trial master file (TMF).

14.5. Reports and Publications

Publication of study results should be followed as presented in the Clinical Trial Agreement (CTA).

14.6. Public Posting of Trial Information

Curatek will register this trial as required by the Food and Drug Administration Modernization Act (FDAMA) Section 113 and the Food and Drug Administration Amendments Act (FDAAA) Section 801. Information posted may include participating investigators' names and contact information.

14.7. Subject Release from the Study

All subjects are free to withdraw from participation in the study at any time, and for whatever reason, specified or unspecified, and without prejudice. The reason for the discontinuation will be entered onto the study termination page of the CRF.

No constraints will be placed on ordinary subject management, and subjects may be placed on other conventional therapy upon request or whenever clinically necessary.

14.8. Sponsor Discontinuation of Study

Premature termination of this study may occur as a result of a regulatory (i.e. FDA) or IRB decision, a drug safety issue, or at the discretion of Curatek. Curatek retains the right to discontinue development of BV, VVC, Combo, and Placebo Gels at any time.

If the study is prematurely terminated, Curatek will promptly notify all investigators. Investigators must then promptly contact all enrolled subjects, as applicable. Final subject evaluations and the collection of study materials as directed by Curatek should be done to the greatest extent possible.

15. References

1. Allsworth JE, Peipert JF. Prevalence of bacterial vaginosis: 2001-2004 National Health and Nutrition Examination Survey data. *Obstetrics and Gynecology* 2007;109(1):114-20.
2. Spiegel CA. Vaginitis/vaginosis. *Clinics in Laboratory Medicine* 1989;9:525-533.
3. Ravel J, Gajer P, Abdo Z, Schneider GM, Koenig SS, McCulle SL, Karlebach S, Gorle R, Russell J, Tacket CO, Brotman RM, Davis CC, Ault K, Peralta L, Forney LJ. Vaginal microbiome of reproductive-age women. *Proceedings of the National Academy of Science*. 2011;108 Suppl 1:4680-7.
4. Gardner HL, Dukes CD. *Haemophilus vaginalis* vaginitis. *American Journal of Obstetrics and Gynecology* 1955;69:962.
5. Zinneman K, Turner GC. The taxonomic position of *Haemophilus vaginalis* (*Corynebacterium vaginale*). *Journal of Pathology and Bacteriology* 1963;85:213-219.
6. Greenwood JR, Pickett MJ. Transfer of *Haemophilus vaginalis* Gardner and Dukes to a new genus *Gardnerella*: *G. vaginalis* (Gardner and Dukes) comb. nov. *International Journal of Systematic Bacteriology* 1980;30:170-178.
7. Spiegel CA, Amsel R, Eschenbach DA, Schoenkebeck R, Holmes KK. Anaerobic bacteria in non-specific vaginitis. *New England Journal of Medicine* 1980;303:601-606.
8. Paavonen J, Miettinen A, Stevens C, Chen KCS, Holmes KK. *Mycoplasma hominis* in non-specific vaginitis. *Sexually Transmitted Diseases* 1983;10:271-275.
9. Srinivasan S, Hoffman NG, Morgan MT, Matsen FA, Fiedler TL, Hall RW, Ross FJ, McCoy CO, Bumgarner R, Marrazzo JM, Fredricks DN. Bacterial communities in women with bacterial vaginosis: high resolution phylogenetic analyses reveal relationships of microbiota to clinical criteria. *PLoS One*. 2012;7(6):e37818.
10. Amsel R, Totten PA, Spiegel CA, Chen KCS, Eschenbach DA, Holmes KK. Nonspecific vaginitis: diagnostic criteria and microbial and epidemiological associations. *American Journal of Medicine* 1983;74:14-22.
11. Nugent RP, Krohn MA, Hillier SL. Reliability of diagnosing bacterial vaginosis is improved by a standardized method of Gram stain interpretation. *Journal of Clinical Microbiology* 1991;29:297-301
12. Centers for Disease Control. Sexually transmitted disease treatment guidelines 2002. *Morbidity and Mortality Weekly Report* 2002;51(RR-6):1-78.
13. Package inserts for MetroGel-Vaginal and Cleocin Vaginal Cream. *Physician's Desk Reference* 2013.
14. Sobel JD. Vaginal infections in adult women. *Sexually Transmitted Diseases* 1990;74:1573-1602.
15. Hurley R, DeLouvois. *Candida* vaginitis. *Postgraduate Medical Journal* 1979;55:645-647.
16. Ringdahl E. Treatment of recurrent vulvovaginal candidiasis. *American Family Physician* 2000;11:3306-3312.
17. Schaff VM, Perez-Stable EJ, Borchart K. The limited value of symptoms and signs in the diagnosis of vaginal infections. *Archives of Internal Medicine* 1990;150:1929-1933.
18. Landers DV, Wiesenfeld HC, Heine P, Krohn MJ, Hillier SL. Predictive value of the clinical diagnosis of lower genital tract infection in women. *American Journal of Obstetrics and Gynecology* 2004;190:1004-1010.
19. Hoffstetter SE, Barr S, LeFevre C, Leong FC, Leet T. Self-reported yeast symptoms compared with clinical wet mount analysis and vaginal yeast culture in a specialty clinic setting. *Journal of Reproductive Medicine* 2008;53(6):402-6.

20. Ferris DG, Hendrich J, Payne PM, Getts A, Rassekh R, Mathis D, Litaker MS. Office based diagnosis of vaginitis. Clinician-performed tests compared with a rapid nucleic acid hybridization test. *The Journal of Family Practice* 1995;41(6):575-581.
21. Petersen CS, Danielsen AG, Renneberg J. Direct or referral microscopy of vaginal wet smear for bacterial vaginosis: experience from and STD clinic. *Acta Dermatologica Venereologica* 1999;79:473-474.
22. Ferris DG, Nyirjesy P, Sobel JD, Soper D, Pavletic A, Litaker MS. Over-the-counter antifungal drug misuse associated with patient-diagnosed vulvovaginal candidiasis. *Obstetrics and Gynecology* 2002;99:419-425.
23. Redondo-Lopez V, Meriwether C, Schmitt C, Opitz M, Cook R, Sobel JD. Vulvovaginal candidiasis complicating recurrent bacterial vaginosis. *Sexually Transmitted Diseases* 1990;17:51-53.
24. Sanchez S, Garcia PJ, Thomas KK, Catlin M, Holmes KK. Intravaginal metronidazole gel versus metronidazole plus nystatin ovules for bacterial vaginosis: a randomized controlled trial. *American Journal of Obstetrics and Gynecology* 2004;191:1898-1906.
25. Jones BM, Geary I, Lee ME, Duerden BI. Comparison of the *in vitro* activities of fenticonazole, other imidazoles, metronidazole, and tetracycline against organisms associated with bacterial vaginosis and skin infections. *Antimicrobial Agents and Chemotherapy* 1989;33(6):970-972.

Appendix A: Schedule of Procedures

Procedure	Baseline Visit	Test of Cure Visit	Follow Up Visit
	Visit 1	Visit 2	Visit 3
		(7-14 days after randomization)	(21-30 days after randomization)
Informed consent signed	X		
Demographic information	X		
Contraceptive, obstetric, & gynecologic history	X		
Medical & surgical history	X		
Physical exam and vital signs	X		
Pelvic Examination			
<ul style="list-style-type: none"> • Symptom and Sign Severity Score <ul style="list-style-type: none"> ○ Evaluate symptoms: itching, burning, and irritation ○ Evaluate signs: edema, erythema, & excoriation 	X	X	X
<ul style="list-style-type: none"> • Visual inspection for genital herpes and warts 	X		
<ul style="list-style-type: none"> • Characterization of vaginal discharge 	X	X	X
<ul style="list-style-type: none"> • Vaginal pH 	X	X	X
<ul style="list-style-type: none"> • KOH “whiff test” 	X	X	X
<ul style="list-style-type: none"> • KOH wet mount—examine for yeast forms 	X		
<ul style="list-style-type: none"> • Saline wet mount— examine for clue cells 	X	X	X
<ul style="list-style-type: none"> • Saline wet mount— examine for motile trichomonads 	X	X	X
Tests/Cultures			
<ul style="list-style-type: none"> • Vaginal Gram stain 	X	X	X
<ul style="list-style-type: none"> • Vaginal Yeast culture 	X	X	X
<ul style="list-style-type: none"> • Tests for <i>N. gonorrhoeae</i>, <i>Chlamydia trachomatis</i>, and <i>Trichomonas vaginalis</i> 	X		
<ul style="list-style-type: none"> • Culture for herpes (if suspected) 	X		
<ul style="list-style-type: none"> • Pap smear (if ≥ 21 yrs and not done within past 3 years) 	X		
<ul style="list-style-type: none"> • Pregnancy test^a 	X		
<ul style="list-style-type: none"> • CBC and blood chemistry^{b, d} 	X	X	X ^c
Inclusion/exclusion criteria	X		
Diagnosis for infection study enrollment	X		
Randomization and dispensation of study drug	X		
Study drug administration and dosing instructions	X		

Procedure	Baseline Visit	Test of Cure Visit	Follow Up Visit
	Visit 1	Visit 2	Visit 3
		(7-14 days after randomization)	(21-30 days after randomization)
Subject instructions/reinforcement of instructions	X	X	
Schedule/confirm next visits	X	X	
Subject Compliance			
• Study instructions		X	X
• Study drug administration/compliance ^d		X	X ^c
Time to symptom resolution/reoccurrence (subject assessment)		X	X ^c
Prior/concomitant medication assessment ^d	X	X	X
Adverse event assessment ^d		X	X
Assessment of Clinical Status: Need for additional treatment for vaginal discomfort/symptoms		X	
Assessment of Clinical Status: Need for additional treatment for vaginal infection			X
Collect returned, unused study drug ^d		X	X ^c
Collect and review diary ^d		X	X ^c
Subject satisfaction survey			X
Study Termination			X

a. Pregnancy test is required if subject is not post-menopausal ≥ 1 year or is not surgically sterile (i.e. hysterectomy bilateral oophorectomy, or bilateral tubal ligation).

b. CBC and blood chemistries to be obtained only for subjects randomized to the Mixed Infection Study.

c. If previously not done at Visit 2; or updated information regarding time to resolution/reoccurrence of symptoms is available.

d. Limited procedures for subjects terminated (at any visit) for the following reason: randomized and later found not to meet eligibility criteria (i.e. positive baseline culture for gonorrhea, chlamydia, trichomoniasis or herpes; Nugent score < 4 for subjects enrolled in the BV or Mixed Infection Study; negative fungal culture for *Candida* for subjects enrolled in the VVC or Mixed Infection Study).

Appendix B: Instructions for Subjects

- You should begin the study drug as soon as possible but not later than two days after your office/clinic visit.
- Insert one applicator of the study drug into your vagina at bedtime for three days in a row. (See the Instructions for Using Study Drug that you have been given.) Do not take any extra drug even there is some left in the tube.
- Do not have sexual intercourse during treatment or before you return for your next visit (Visit 2).
- You should not become pregnant while you are in the study, and if you are heterosexually active you must be on an acceptable method of birth control throughout the study.
- Do not use any intravaginal/vulvovaginal products (except your study drug) during treatment or before you return for your next visit (Visit 2). You should also not use any intravaginal/vulvovaginal products within 48 hour of your final visit (Visit 3). Examples of products you should not use include feminine deodorants and douches; spermicidal creams, gels, and foams; vaginal lubricants, moisturizers, and hormonal suppositories and creams such as Vagifem®, Estrace® and Premarin® cream; and tampons. You should try not to use any of these products during the entire time you are in the study.
- Do not take any systemic (i.e. oral, IV, or IM) or intravaginal/vulvovaginal antifungal (yeast), antimicrobial (antibiotics), corticosteroid, or immunosuppressant medicine while you are in the study.
- Do not ingest alcohol or propylene glycol during treatment and for 1 day thereafter.
- If you start or stop any medicines different than what you were taking when you started the study, let the study doctor or study staff know.
- If you have sexual intercourse within 48 hours of your last scheduled visit, have your partner use a non-lubricated condom.
- Complete the diary that was given to you and return it at your next visit (Visit 2).
- After you finish taking your study drug, place the drug tube (and any remaining drug) inside the packaging given to you. Seal the package and return it at your next visit (Visit 2). Do not return the applicators.
- If you are concerned about any possible side effects or if your symptoms continue to bother you, you may call the office/clinic to be evaluated.

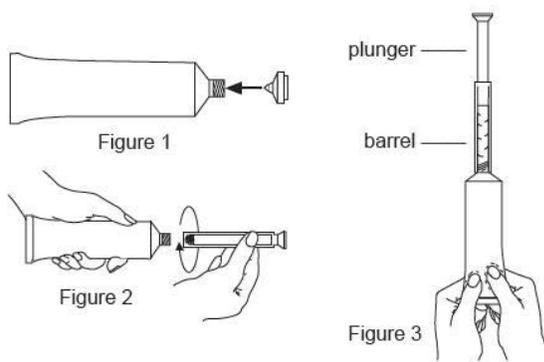
Appendix C: Instructions for Using Study Drug

Instructions for Using Your Study Drug

Insert one applicatorful of the study drug you received into your vagina at bedtime for 3 days in a row.

Filling the Applicator

1. Remove the cap from the tube and puncture the seal on the drug tube (if necessary) with the pointed tip of the cap (Figure 1).
2. Screw the applicator onto the tube (Figure 2).
3. Slowly squeeze the tube from the bottom until the applicator is full. The plunger will stop when the applicator is full (Figure 3).
4. Unscrew the applicator and replace the cap on the drug tube.



Inserting the Applicator

1. Lie on your back with your knees drawn up (or any position that is comfortable for you). Hold the filled applicator by the barrel and gently insert it into your vagina as far as it will comfortably go (Figure 4)
2. Slowly press the plunger until it stops to deposit all of the study drug in the applicator into the vagina.
3. Withdrawal the applicator. Discard the applicator after each use.

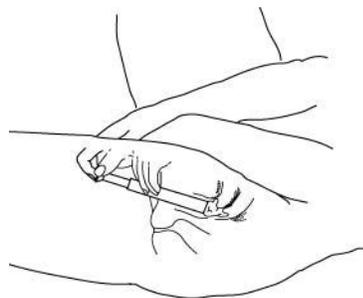


Figure 4

5. Did you experience any side effects while you were in the study? Side effects may be local in the vaginal area or they may be in other places of your body. Circle your answer. Yes or No

- If **No**, you are finished filling out this diary.
- If **Yes**, enter on the lines below what side effects you experienced, when they started and stopped, and how severe they were.

Side Effect	Date Started	Date Stopped	Severity 1=Mild 2=Moderate 3=Severe

Appendix E: Subject Satisfaction Survey

Subject Satisfaction Survey

(To be completed by subject at final visit)

This questionnaire asks about your experience with the study medicine. It will help Curatek Pharmaceuticals, LLC know what you thought about the medicine you took. Please circle your answer to each question. When you are finished, please initial the bottom of the page.

1. Have you ever used intravaginal medicine(s) before (for example over the counter yeast medicines like Monistat or Gyne-Lotrimin, etc.)? **YES NO**
 - If yes, go to question 2.
 - If no, skip to question 3.

2. How would you rate the medicine you used in this study compared to vaginal medicine(s) you used in the past? **BETTER WORSE SAME**

3. On a scale of 1 to 5, how would you rate your satisfaction with the study drug? (The lower the number, the less satisfied you were; the higher the number the more satisfied you were.)

1	2	3	4	5
Very Dissatisfied	Somewhat Dissatisfied	Neither Satisfied Nor Dissatisfied	Satisfied	Very Satisfied

Did any of the following things bother you?

- Leaking study drug? **YES NO**
 - Greasy feeling? **YES NO**
 - Stains in underwear? **YES NO**
4. If you had the same infection again, would you like to be treated with this drug again? **YES NO**