Identifiers: **NCT02308046**

NCT02308033

NCT02308007

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

Brief Title: Multi-Center Study of New Medications to Treat Vaginal Infections

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

Document: Statistical Analysis Plan

Date of Document: May 1, 2018

Sponsor: Curatek Pharmaceuticals, LLC

[redacted] [redacted]

Protocol Number: MTC-001

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

Phase III

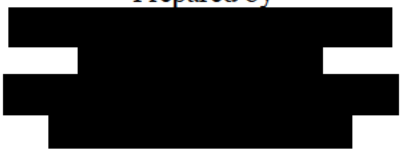
Statistical Analysis Plan

Version 1.0
Final: May 1, 2018

Sponsor:

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

Prepared by



Confidential

Protocol #MTC-001

IND # 121,229
124,679
124,680

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

Signatures

Statistical Analysis Plan (SAP) Approval Form

Statistician [redacted] 5/1/18
Date

Project Scientist [redacted] 5/1/2018
Date

Table of Contents

1. INTRODUCTION

Name of Sponsor
Curatek Pharmaceuticals, LLC

Active Ingredient(s) and Dose of Investigational Products
- BV Gel: 0.9% metronidazole gel (45 mg of metronidazole/5 grams of gel)
- VVC Gel: 0.8% terconazole gel (40 mg of terconazole/5 grams of gel)
- Combination Gel: 0.9% metronidazole gel and 0.8% terconazole gel (45 mg metronidazole and 40 mg of terconazole/5 grams of gel)

Protocol Number
MTC-001

This analysis plan describes the statistical techniques that will be used to assess the efficacy, safety, and tolerability of BV Gel, VVC Gel, and Combo Gel, in subjects diagnosed with bacterial vaginosis (BV), vulvovaginal candidiasis (VVC), or concurrent BV and VVC (Mixed Infection). The formats for the tables, listings, and figures described in this SAP are provided in a companion document.

The study has been conducted as Protocol MTC-001, finalized December 12, 2014 and amended on March 12, 2015. No subjects were enrolled under the protocol finalized on December 12, 2014 and there have been no previous statistical analysis plans.

1.1 Study Objectives

There are three primary objectives of the trial; one for each product/indication. They are to:
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 infections)

1.2 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 applicator 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.

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.

The study consists of three visits: a Screening and Enrollment/Baseline visit (visit 1), a Test of Cure visit (visit 2) and one follow-up clinic visit (visit 3). Visit 2 will occur 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. Visit 3 will occur 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 at Visit 3.

2. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

2.1 Changes in the Conduct of the Study

The original protocol was version 1.0 and dated December 12, 2014. There has been one revision to the protocol, numbered version 2.0 and dated March 12, 2015, as of the development of this Statistical Analysis Plan (SAP). Changes per the revision are incorporated in this SAP.

2.2 Changes from the Analyses Planned in the Protocol

This analysis plan details analyses to be conducted for the study. Some of the analyses detailed here may be more explicit or in some aspects different than those stated in the protocol. In case of differences, this SAP supersedes the statistical sections in the protocol.

3. STUDY OBSERVATIONS

The evaluation of subject eligibility will occur at the Baseline visit (visit 1). Eligible subjects will receive a maximum duration of treatment of three days and a maximum trial duration of 30 days from the time of randomization. The test of cure visit (visit 2) will occur 7-14 days after randomization. If the subject did not need additional treatment for vaginal discomfort/symptoms (and the subject did not self-medicate), the subject will be asked to return 21-30 days after randomization (visit 3).

3.1 Screening/Baseline Evaluations

Baseline (visit 1) medical evaluations will include:

- Medical and surgical history
- Contraceptive/obstetric status and gynecologic history
- Use of concomitant medications (i.e. current and within 30 days of enrollment) as well as treatments for BV and/or VVC infections within the past year
- 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.
- General physical examination and vital signs
- Laboratory tests
  - 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

Baseline (visit 1) pelvic examination and specimen collections will include:

- 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.
- KOH Whiff Test
- KOH and saline wet mounts
- Vaginal Candida culture: Obtain a Candida culture as specified in the central laboratory manual utilizing the collection and shipment supplies provided.
- Vaginal Gram Stain: Obtain a Gram Stain as specified in the central laboratory manual utilizing the collection and shipment supplies provided.
- Papanicolaou smear: Obtain a Pap smear if subject is ≥ 21 years old and has not had one within the past 3 years.
- Test for Neisseria gonorrhoeae, Chlamydia trachomatis, and Trichomonas vaginalis as specified in the central laboratory manual utilizing the collection and shipment supplies provided.
- Culture for Herpes simplex (only if suspected).

3.2 Test of Cure Visit (Visit 2) Evaluations

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.

- Review of Diary
- Assessment of Compliance: Subjects are queried to determine compliance with study drug administration and study instructions.
- 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.
- 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.
- 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

o Pelvic Examination and Specimen Collections
- Vulvovaginal signs rating
- Vaginal discharge characterization
- Vaginal pH measurement
- KOH Whiff Test
- Saline wet mount
- Vaginal Candida culture
- Vaginal Gram stain

o 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. 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).

o Determination of Cure or Failure of Subject's Enrolled Infection:
- BV subjects must satisfy all three of the clinical criteria listed below in order to be considered a BV cure (i.e. clinical cure).
  - Discharge has returned to normal/physiologic[1]
  - 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[2].

- VVC subjects must have all signs and symptoms attributable to VVC resolved (i.e. clinical cure), in order to be considered a VVC 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[2].
- 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.

1. 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.
2. Self-administration of therapy includes prescription and OTC antimicrobial, anti-fungal, analgesics, or steroid treatments.

3.3 Follow Up Visit (Visit 3) Evaluations

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.

- Assessment of Compliance: Subjects are queried to determine compliance with study drug administration and study instructions.
- 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.
- Laboratory Tests and Specimen Collections: The lab tests listed below will be obtained at Visit 3.
  - Vaginal culture for Candida species
  - Vaginal Gram stain
- Pelvic Examination and Specimen Collections
  - Vulvovaginal signs rating
  - Vaginal discharge characterization
  - Vaginal pH measurement
  - KOH Whiff Test
  - Saline wet mount
  - Vaginal Candida culture
  - Vaginal Gram stain
- 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.
- Subject Satisfaction Survey: Subjects should be given the Subject Satisfaction Survey and asked to complete the form before leaving the clinic. Completion of the survey is voluntary and does not affect participation in the study in any way.

3.4 Limited Termination 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).

4. STATISTICAL METHODS

The following is a detailed proposal of the statistical summaries planned for subject data collected during the trial. 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.

4.1 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 that are repeated out of schedule, such as repeat laboratory tests, the last measurement within a scheduled time interval (i.e. days 7 – 14 for Visit 2 and days 21 – 30 for Visit 3) 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).
5. 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).

4.2 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 also be conducted on the per protocol (PP) population. The data analysis populations are defined as:

- ITT: The intent-to-treat population 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. Subjects who are Lost to Follow-up and for whom there is no documentation to ascertain whether or not they were administered treatment will be excluded from the mITT population.
    - In addition, to be included in the mITT population 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.
    - Subjects randomized to treatment but whose baseline laboratory tests subsequently reveal positive results for *Trichomonas vaginalis, Chlamydia trachomatis,* and/or *Neisseria gonorrhoeae* will be excluded from the mITT population.
- PP: The per protocol population 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.
- Safety: The safety population will include all subjects randomized to treatment and administered at least one dose of study drug.

Major protocol deviations (i.e. deviations likely to bias assessment of the primary efficacy measure) that will be used to assess inclusion in the PP population will be determined and reviewed by the Sponsor prior to unblinding the data.

4.3 Efficacy Endpoints and Evaluations

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

Primary Endpoints

- BV Study: BV cure rate, with cure defined as normal/physiologic discharge, negative whiff test, and < 20% clue cells (i.e. clinical cure)
- VVC Study: VVC cure rate, with cure defined as resolution of all signs and symptoms attributable to VVC (i.e. clinical cure)
- 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 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. If this occurs, the subject will remain evaluable for the mITT analyses but will be non-evaluable for the PP analysis.

Secondary Endpoints

Note, for BV a Gram stain Nugent score cure will be defined as a score of < 4, i.e. 0 – 3.

- BV Study: BV clinical and Gram stain Nugent score combined cure rate, and Gram stain Nugent score cure rate alone; changes/improvements in Amsel criteria and Nugent scores; time to resolution of symptoms
    - In addition, cure rates over time will be explored
- VVC Study: VVC clinical and mycologic cure rates combined and mycologic cure alone; 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

4.4 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. 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.

4.5 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 (.45-.55)
    b. Placebo Gel: .20 (.15-.25)
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 (.30-.40)
    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 are true for the population, 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 Patients, by Infection Study and Treatment Group							
Study:	***BV Only Patients***		***VVC Only Patients***		***Mixed Infection Only Subjects***		
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. [redacted]

[redacted]

4.6 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 (but not all) 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 and thus not included in the PP population. Any patients with all data missing will also be non-evaluable.

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

If adverse event start dates are missing or incomplete, the following rules will apply for determining if an event is to be considered treatment emergent. If start date is completely missing, start date will be set as same day as start of treatment and assumed to be at a time following subject's first dose. If start date is incomplete, the date closest to start of treatment will be assumed, without compromising the incomplete data available for the start date.

If study medication start dates are missing or incomplete, the following rules will apply for determining inclusion in the Safety population. If the start date is completely missing and there is no documentation indicating that the patient used study medication, the date will be left as missing and the patient will be excluded from the Safety population. If the start date is completely missing or incomplete and there *is* documentation that indicates the patient used study medication, the date will be imputed to the earliest date and time post-randomization that is consistent with the partial data, and the patient will be included in the Safety population.

4.7 Efficacy Analyses

4.7.1 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 4.3.

Subjects in all studies will be categorized as cure or failure for the 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 and Wald continuity corrected confidence intervals. 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, if all expected cell counts are not at least 5, Fisher's Exact test and confidence intervals using the method of Chan and Zhang (1999) will be used.

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.

Efficacy analysis will not be done for the ITT population, as subjects in the BV and Mixed studies who do not have a gram stain ≥ 4, or subjects in the VVC and Mixed studies who do not have a positive yeast culture, are not evaluated for efficacy. These subjects do not return for Visit 2; rather, they have the Limited Termination visit for safety evaluations only.

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.

4.7.2 Secondary Efficacy Analyses

Secondary efficacy endpoints are listed in Section 4.3. 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 that 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 using the continuity corrected Wald intervals when Chi-square tests are appropriate, or the method of Chan and Zhang (1999) otherwise.

Secondary endpoints that 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 by arm using log-rank tests to compare arms within each study and Kaplan-Meier plots. Kaplan-Meier estimates of the quartiles for time to resolution will be computed, along with 95% confidence intervals. Censoring times for the Kaplan-Meier estimates will be based on the date of last contact or visit 3 (whichever is earliest) if symptoms never resolved or the patient was an early withdrawal and status is unknown.

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).

In addition, for each study a summary will be made of subjects classified as:

- Persistent Infection – no cure at Visit 2 or Visit 3
- Persistent Cure – cure at Visit 2 and Visit 3
- Late Cure – no cure at Visit 2 but cure at Visit 3
- Recurrence – cure at Visit 2 but no cure at Visit 3

A descriptive analysis of the primary endpoint (cure rate) for BV subjects will be performed to assess the impact of loss of potency of the BV gel over time. The proportion of patients achieving a cure will be computed among cohorts of patients completing Visit 2 during each month the study was underway. These proportions will be tabulated by month for the BV Gel arms of the BV study and the mixed infection study. In addition, a plot of the proportions by month will be presented.

4.7 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 4.2, and will be summarized for each treatment group. These summaries will be presented separately for each infection study. In addition, adverse events and laboratory evaluations, 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.

4.8.1 Adverse Events

Adverse events will be coded by system organ class and preferred term using the 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 by system organ class and preferred term, counting proportions of the patients who experienced at least one such adverse event. Frequencies of patients 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 medication.

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, counter measures taken, and outcome will also be produced as warranted. At the least, incidence of drug discontinuation and death will be summarized.

4.8.2 Laboratory Assessments

CBC with differential and blood chemistry data will be collected in the Mixed Infection study only. Values 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.

A shift table will be provided, which will 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.

Mixed Infection Study

Endpoint	Treatment	Baseline	Visit 2/EndStudy		
			Low (L)	Normal (N)	High (H)
BUN	BV Gel	Low (L)	xx	xx	xx
		Normal (N)	xx	xx	xx
		High (H)	xx	xx	xx
		n	xxx		
	VVC Gel				
			Low (L)	Normal (N)	High (H)
		Low (L)	xx	xx	xx
		Normal (N)	xx	xx	xx
		High (H)	xx	xx	xx
		n	xxx		
	Combo Gel				
			Low (L)	Normal (N)	High (H)
		Low (L)	xx	xx	xx
		Normal (N)	xx	xx	xx
		High (H)	xx	xx	xx
etc		n	xxx		

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

4.8.3 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.

4.8.4 Physical Exams

All physical exam data will be presented in listings.

5. REFERENCES

Chan, I.S.F., Zhang, Z., (1999). "Test-Based Exact Confidence Intervals for the Difference of Two Binomial Proportions." Biometrics **55**: 1202-1209.

14. LIST OF TABLES, FIGURES, AND LISTINGS

LIST OF TABLES AND FIGURES

14.1 Demographic and Study Conduct Summaries

14.2 Efficacy Summaries

14.3 Safety Summaries

LIST OF LISTINGS

16.1 Demographic and Study Conduct Listings

Listing 16.1.11 Baseline Physical Exam
Listing 16.1.12 Diagnosis
Listing 16.1.13 Inclusion/Exclusion Criteria Waivers
Listing 16.1.14 Investigator Comments/Protocol Violations
Listing 16.1.15 Randomization and Kit Number
Listing 16.1.16 Concomitant Medications

16.2 Efficacy Listings

Listing 16.2.1 Compliance Assessment
Listing 16.2.2 Tests/Cultures Taken
Listing 16.2.3 Symptom and Sign Severity Score
Listing 16.2.4 Pelvic Exam
Listing 16.2.5 Need for Additional Treatment
Listing 16.2.6 Test-of-Cure
Listing 16.2.7 Symptom Resolution/Recurrence

16.3 Safety Listings

Listing 16.3.1 Study Drug Administration
Listing 16.3.2 Study Drug Compliance
Listing 16.3.3 Adverse Events
Listing 16.3.4 Adverse Events Resulting in Early Termination from the Study
Listing 16.3.5 Adverse Events Resulting in Death
Listing 16.3.6 Lab Values