Title:	A Multicenter, Randomized, Double-Blind, Vehicle-Controlled Study Evaluating the Therapeutic Equivalence and Safety of GDC-229 (Investigational Metronidazole 0.75% Vaginal Gel) and Metronidazole 0.75% Vaginal Gel in the Treatment of Bacterial Vaginosis
Protocol Number:	GDC-229-002
Clinical Phase:	Bioequivalence Study with Clinical Endpoint
Sponsor:	Gage Development Company, LLC [redacted]
Program Manager:	[redacted] Gage Development Company, LLC
Protocol Version:	Version 01.00
Clinical Research Organization:	[redacted]

[redacted]

PROTOCOL SIGNATURE PAGE

Title: A Multicenter, Randomized, Double-Blind, Vehicle-Controlled Study Evaluating the Therapeutic Equivalence and Safety of GDC-229 (Investigational Metronidazole 0.75% Vaginal Gel) and Metronidazole 0.75% Vaginal Gel in the Treatment of Bacterial Vaginosis

Protocol Number: GDC-229-002

Clinical Phase: Bioequivalence Study with Clinical Endpoint

Sponsor: [redacted]

23 Jan 2017
Date

1-23-2017
Date

24 JAN 2017
Date

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PROTOCOL SYNOPSIS

Title:	A Multicenter, Randomized, Double-Blind, Vehicle Controlled Study Evaluating the Therapeutic Equivalence and Safety of GDC-229 (Investigational Metronidazole 0.75% Vaginal Gel) and Metronidazole 0.75% Vaginal Gel in the Treatment of Bacterial Vaginosis
Phase of Development:	Bioequivalence Study with Clinical Endpoint
Sponsor:	Gage Development Company, LLC
Protocol Number:	GDC-229-002
Indication:	Treatment of Bacterial Vaginosis (BV)
Study Population:	Adult females presenting with BV who meet all of the four Amsel's Diagnostic Criteria (defined below in Inclusion Criteria) at the Screening Visit
Objectives:	The primary objective is to assess the therapeutic equivalence of an experimental formulation of a metronidazole 0.75% vaginal gel (GDC-229; test product) versus metronidazole 0.75% vaginal gel (Oceanside Pharmaceuticals) in subjects with BV. A vehicle (placebo) arm is included for assay sensitivity. The secondary objective is to evaluate the safety and tolerability of an experimental formulation of a metronidazole 0.75% vaginal gel (GDC 229; test product) versus metronidazole 0.75% vaginal gel (Oceanside Pharmaceuticals) and vehicle (placebo) in subjects with BV.
Endpoints:	Primary Endpoint: The proportion of subjects achieving a clinical cure at the Test of Cure Visit (V3) defined as follows: • Return to normal physiological discharge as assessed by the investigator • Negative 10% potassium hydroxide (KOH) whiff test • Presence of clue cells at < 20% of the total epithelial cells on microscopic examination of the saline wet mount Supportive Secondary Endpoints: • Nugent score of < 4 at Visit 3 • Responder outcome (therapeutic cure) defined as follows: o Clinical cure as defined in the Primary Endpoint o Vaginal pH < 4.7 at Visit 3 o Nugent score of < 4 at Visit 3 (Bacteriological Cure)
Identity of Study Treatment(s):	GDC-229 (metronidazole 0.75% vaginal gel; test product) Marketed metronidazole 0.75% vaginal gel (Oceanside Pharmaceuticals); reference product Placebo (i.e., vehicle gel)

Projected Number of Sites:	Approximately 40
Countries or Regions:	US only
Expected Number of Subjects:	738 (enrolled)
Rationale, Background, Risks and Benefits:	Bacterial vaginosis (BV) is a common vaginal infection in women. Untreated BV may lead to higher risk of a sexually transmitted infection or pregnancy problems. Symptoms of BV may include unusual vaginal discharge, burning when urinating, itching around the outside of the vagina, and vaginal irritation. Antibiotics are used to treat BV. Metronidazole was approved for use in the US in 1963 and is currently a first-line treatment for BV. Gage Development Company, LLC is developing a drug product candidate that is designed to be therapeutically equivalent to the marketed drug metronidazole 0.75% vaginal gel for the treatment of BV. The contraindications, warnings, precautions, drug interactions, and adverse events (AEs) associated with the use of metronidazole are described in the approved product labeling for metronidazole 0.75% vaginal gel (Oceanside Pharmaceuticals).
Study Design:	This is a multicenter, randomized, double-blind, vehicle-controlled, bioequivalence clinical endpoint study evaluating the therapeutic equivalence, safety, and tolerability of GDC-229 (test product), the reference product metronidazole 0.75% vaginal gel (Oceanside Pharmaceuticals), and placebo (vehicle gel) in subjects with BV. The study is approximately 30 days in duration and is comprised of three study visits: Entry Visit (Visit 1; day of screening and randomization), Post-Treatment Assessment Visit (Visit 2; 7 to 14 days after randomization), and Test of Cure (Visit 3; 21 to 30 days after randomization). At the Entry Visit (Visit 1), the following should be collected/assessed: review of all inclusion and exclusion criteria, demographic information, gynecological history, and medical history (including concomitant medications used up to 30 days prior to screening), physical and pelvic examination, vital signs, microbiological specimen collection for Nugent's score assessment and cervical infections (e.g., *Chlamydia trachomatis, Neisseria gonorrhoeae*), urine drug screening, and urine pregnancy test. Diagnosis of BV will be determined based on Amsel's criteria, which requires presence of all four of the following: off-white (milky or gray), thin homogeneous discharge with minimal or absent pruritus and inflammation of the vulva and vagina; vaginal pH > 4.5; fishy odor upon addition of KOH to vaginal fluid (positive whiff test); and presence of clue cells on saline wet mount greater than or equal to 20% of total epithelial cells on microscopic examination of the saline wet

	mount. If the results of the Amsel's diagnosis exam are positive and the subject meets all other inclusion and exclusion criteria, the subject will be randomized to treatment. Note: Nugent's result is not used for randomization decisions. Eligible women will be randomized 1:1:1 to receive GDC-229 (investigational metronidazole 0.75% vaginal gel), marketed metronidazole 0.75% vaginal gel (Oceanside Pharmaceuticals) or placebo. Subjects will be instructed to administer treatment intravaginally once daily at bedtime during Days 1-5. At Post-Treatment Assessment (Visit 2), 7 to 14 days after randomization (Visit 1), the following procedures will be performed: pelvic examination, and collection of study medication, subject-reported and Investigator-assessed local site reactions, AEs, and concomitant medications. At this visit, subjects will be examined to assess for resolution of the following Amsel's criteria: resolution of the abnormal vaginal discharge, negative KOH whiff test, and the presence of clue cells at less than 20 percent of the total epithelial cells on microscopic examination of the saline wet mount; in addition, the vaginal pH will be tested to assess if it has returned to the normal range of < 4.7. The Test of Cure (Visit 3) will be conducted 21 to 30 days after Visit 1 to assess if the subject displays presence of normal vaginal discharge, absence of fishy odor using KOH whiff test, and less than 20% clue cells on microscopic examination of a wet saline wet mount; in addition, the vaginal pH will be tested to assess if it has returned to the normal range of < 4.7. At this visit, the following procedures will be performed: a physical examination, including a pelvic exam to assess for the above Amsel's criteria and for microbiological specimen collection for Nugent's score assessment; urine pregnancy test, subject-reported and Investigator-assessed local site reactions, and assessment of observed or subject-reported AEs and concomitant medications.
Inclusion Criteria:	Subjects meeting all of the following criteria may be considered for study participation: 1. Non-pregnant female aged ≥ 18 years who is in good general health 2. Diagnosis of BV, defined as presence of all of the following: a. Clinical diagnosis of BV (e.g., off-white [milky or gray], thin homogeneous discharge with minimal or absent pruritus and inflammation of the vulva and vagina); AND b. Saline wet mount of vaginal discharge demonstrating the proportion of clue cells to be ≥ 20% of the total epithelial cells; AND c. Vaginal secretion pH > 4.5, using pH paper that measures from 4.0 to 6.0; AND

	d. Positive (fish odor) "whiff test" after addition of a drop of 10% KOH to vaginal discharge. 3. Willing to refrain from vaginal sexual intercourse on Days 1 to 7 (i.e., during treatment and for two post-treatment days) and for 48 hours prior to Visits 2 and 3. 4. Willing to refrain from using any intravaginal product (e.g., spermicide, tampon, douche, feminine deodorant spray, diaphragm, vaginal ring birth control, or condom with spermicide or insertion into the vagina of any drug or non-drug product during treatment), other than study treatment for the duration of the trial. 5. Subjects of childbearing potential who have a negative urine pregnancy test at the Entry Visit (Visit 1) and agree to use an acceptable form of birth control throughout the study. Acceptable forms of birth control include oral contraceptives (the pill), intrauterine devices (IUDs), contraceptive implants under the skin, patches or injections, and condoms without spermicide. Oral or transdermal hormonal contraceptives must be in use for one full cycle (e.g., four to eight weeks) prior to test article application. Injectable or implanted contraceptives (e.g., Depo-Provera, Nexplanon, or hormonal IUD) must be injected/inserted at least seven days prior to test article application. Subjects who are not of childbearing potential, as defined below, must also have a negative urine pregnancy test prior to randomization: a. Postmenopausal for at least one year prior to the Entry Visit (Visit 1) (defined as ≥ 50 years of age and amenorrheic for > one continuous year) or b. Surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) at least 6 months before first dose or c. Non-surgical permanent sterilization (e.g., Essure® procedure) procedure at least 3 months prior to first dose 6. The subject is willing to refrain from alcohol intake on study Days 1 to 6 (i.e., during treatment through first post-treatment day). 7. Able to understand and willing to sign the informed consent form (ICF) and able to comply with the requirements of the protocol.
Exclusion Criteria:	Subjects meeting any of the following criteria will be excluded: 1. Known current or recent history (i.e., within the past two years prior to the Entry Visit) of alcohol or substance abuse.

[redacted]

	2. Experienced a clinically significant medical event within 90 days prior to the Entry Visit (e.g., stroke, myocardial infarction, surgery). 3. Abnormal pap or high risk human papillomavirus (HPV) within the last three months requiring colposcopic evaluation or treatment (e.g., cryotherapy, loop electrosurgical excision procedure [LEEP], or conization of the cervix). 4. History or presence of clinically significant central nervous system (CNS), cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, gynecologic, dermatologic, neurologic, oncologic, or psychiatric disease, or any other condition that, in the opinion of the Investigator, would jeopardize the safety of the subject or the validity of the study results. 5. Pregnant, lactating, or planning to become pregnant or breastfeed during the study period. 6. Menstruating when diagnosis of BV is determined at the Entry Visit (Visit 1). 7. Primary or secondary immunodeficiency. 8. History of severe liver disease. 9. History of CNS-related disorders. 10. Evidence of any vulvovaginitis at screening other than BV (e.g., vulvovaginal candidiasis, *Trichomonas vaginalis, Chlamydia trachomatis, Neisseria gonorrhoeae, active* herpes simplex, or active HPV). 11. At the Entry Visit, the subject is receiving any antibacterial therapy unrelated to BV. 12. Subject has received vaginal therapy within two weeks prior to the Entry Visit, or plans to receive vaginal therapy for the duration of the trial. 13. Subject is or will be undergoing treatment for cervical intraepithelial neoplasia (CIN) or cervical carcinoma. 14. History of hypersensitivity or allergy to metronidazole, parabens, other nitroimidazole derivatives, or other ingredients of the GDC-229 (metronidazole 0.75% vaginal gel), metronidazole 0.75% vaginal gel (Oceanside Pharmaceuticals), or vehicle gel. 15. Use within 2 weeks prior to the Entry Visit of 1) disulfiram, 2) lithium, 3) topical or systemic antibiotics, or 4) topical or systemic antifungals. 16. Use of spermicides, tampons, douches, diaphragms, condoms or other intravaginal product within 48 hours prior to dosing on study Day 1. 17. Current use of anticoagulation therapy or cimetidine. 18. Participating in a clinical trial involving an investigational product within the 30 days prior to the Entry Visit (Visit 1) or is planning to participate in another clinical trial during this study.
Safety Parameters:	The following safety parameters will be collected:

[redacted]

	• Urine pregnancy test at every site visit • Urine drug screen (Visit 1) • Medical and gynecological history (Visit 1) • Physical exam (Visits 1 and 3) and pelvic examinations (Visits 1, 2, and 3) • Vital sign assessments including oral temperature, sitting blood pressure, heart rate, and respiratory rate (Visits 1, 2, and 3) as well as weight (Visits 1 and 3) • AE and concomitant medications reporting (Visits 1, 2, and 3) • Local site reaction assessments (subject-reported and Investigator-assessed at Visits 2 and 3) • Screening for *Chlamydia trachomatis, Neisseria gonorrhoeae* (Visit 1)
Efficacy Evaluations:	Primary: Clinical cure defined as return to normal physiological discharge, negative whiff test, and the presence of clue cells at <20% of the total epithelial cells on microscopic examination of the saline wet mount at Test of Cure (Visit 3; Day 21-30). Secondary: Bacteriological Cure defined as: Nugent's score <4 at Visit 3 (Day 21-30). Therapeutic cure defined as: having achieved clinical cure, vaginal pH of <4.7, and bacteriological cure.
Other Assessments:	Demographic characteristics will be collected.
Statistical Considerations:	The following assumptions were considered for the power and sample size assessment: • the proportion of participants in the test and reference arms achieving a clinical cure is at least 36% and within 4% of each other, • the proportion subjects receiving placebo that achieves clinical cure is 20% and • 12.4% of randomized subjects do not qualify for the modified Intent-to-Treat (mITT) population, Based on the above assumptions 603 subjects will be required. However, the previous studies that were used to estimate effect size had significant differences in study design and definition of primary endpoint. Taking these differences into consideration, 738 subjects will be randomized to achieve at least 90% power for superiority and bioequivalence. <u>Analysis Datasets</u> <u>Intent-to-Treat (ITT) Population</u>: All randomized subjects.

[redacted]

	Safety Population: All randomized subjects who receive at least 1 dose of study drug. Modified Intent-to-Treat (mITT) Population: All randomized subjects excluding those who subsequently demonstrate a positive test result for other concomitant vaginal or cervical infections at baseline (e.g. *C. trachomatis*, *N. gonorrhoeae*) which may interfere with the efficacy assessment for BV or who have a baseline Nugent score<4, received study treatment, and returned for at least one post-baseline visit. Per Protocol (PP) Population: Includes all subjects who qualify for the mITT population and who follow important components of the trial (including subjects who adhere to treatment and follow-up for efficacy within the prescribed timeframe). Subjects in the mITT population who discontinue early from the study and do not have an assessment of clinical cure and bacteriological cure will be included in the mITT population analyses as treatment failures. These subjects without outcomes, but are classified as treatment failures will not be included in the PP analyses. To establish bioequivalence, the 90% confidence interval for the primary endpoint (the difference [test-reference] in proportion of subjects achieving a clinical cure) must be within [-0.20, +0.20], using the PP population. As a parameter for determining adequate study sensitivity, the test product and the reference drug should both be statistically superior to placebo ($p<0.05$, two-sided) for the primary endpoint, using the mITT study population.
Duration of Treatment:	Subjects will be treated on Days 1 to 5 with Visit 2 to occur between Days 7 and 14 (inclusive). Test of Cure (Visit 3) will occur between Days 21 and 30 (inclusive) after randomization to assess the primary and secondary endpoints.
Study Duration:	Approximately eight months for recruitment and completion of study subject participation.
Compliance:	The trial will be carried out in accordance with Good Clinical Practice (GCP) as required by the following: United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Parts 50, 54, 56, 312, and320), ICH E6, and the 2013 revision of the Declaration of Helsinki.

[redacted]

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
BV	Bacterial vaginosis
CDC	Centers for Disease Control and Prevention
CNS	Central nervous system
CRO	Clinical research organization
CFR	Code of Federal Regulations
CV	Curriculum Vitae
eCRF	Electronic case report form
EDC	Electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
hCG	Human chorionic gonadotropin
HPV	Human papillomavirus
ICF	Informed consent form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine device
KOH	Potassium hydroxide
LEEP	Loop electrosurgical excision procedure
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
NDA	New Drug Application
PP	Per protocol
SAE	Serious adverse event
STI	Sexually transmitted infection
SOP	Standard operating procedure
US	United States

[redacted]

1 INTRODUCTION AND BACKGROUND

Bacterial vaginosis (BV) is a common vaginal infection in women. The risk of plasma cell endometritis in women with BV has been reported to be 15 times higher than the risk in women without BV (Korn 1995). The presence of atypical cells on a Pap smear is also more common in women with BV (Eltabbakh 1995). Untreated BV can lead to higher risk of contracting a sexually transmitted infection (STI) or lead to pregnancy problems (CDC Fact Sheet).

Symptoms of BV may include unusual vaginal discharge, burning when urinating, itching around the outside of the vagina, and vaginal irritation. BV is typically diagnosed using Amsel's criteria (Amsel 1983). The four Amsel's criteria used to determine a clinical diagnosis of BV are as follows: vaginal pH > 4.5; positive "whiff" test ("fishy" odor); homogenous, nonviscous, off-white (milky or gray) discharge; and the presence of ≥ 20% clue cells.

Oral and topical antibiotics are used to treat BV. Metronidazole was approved for use in the U.S. in 1963 and is currently a first-line treatment for BV (Flagyl NDA). Gage Development Company, LLC is developing a drug product candidate that is designed to be therapeutically equivalent to the marketed drug metronidazole 0.75% vaginal gel for the treatment of BV.

2 STUDY OBJECTIVES

Primary Objective:

The primary objective of this study to assess the therapeutic equivalence of an experimental formulation of a metronidazole 0.75% vaginal gel (GDC 229; test product) versus metronidazole 0.75% vaginal gel (Oceanside Pharmaceuticals) in subjects with BV. A vehicle (placebo) arm is included for assay sensitivity.

Secondary Objectives:

The secondary objective of this study is to evaluate the safety and tolerability of an experimental formulation of a metronidazole 0.75% vaginal gel (GDC 229; test product) versus metronidazole 0.75% vaginal gel (Oceanside Pharmaceuticals) and vehicle (placebo) in subjects with BV.

3 INVESTIGATIONAL PLAN

3.1 Description of Overall Study Design and Plan

This is a multicenter, randomized, double-blind, vehicle-controlled, bioequivalence clinical endpoint study to evaluate the therapeutic equivalence, safety, and tolerability of an experimental formulation of a metronidazole 0.75% vaginal gel (GDC-229; test product) and the reference product, metronidazole 0.75% vaginal gel (Oceanside Pharmaceuticals) in generally healthy adult subjects with BV. The study is 30 days in duration, including a 5-day treatment period. There are three study visits as shown in Table 1: Entry Visit (Visit 1, day of screening and randomization); Post-Treatment Assessment (Visit 2, 7 to 14 days after randomization), and Test of Cure (Visit 3, 21 to 30 days after randomization). Including a recruitment period of seven months, the total study duration is approximately eight months.

Table 1 Visit Descriptors

Visit Number	Visit Name and Purpose	Day of Study
Visit 1	Screening and Randomization	Day 1
Visit 2	Post-Treatment Assessment	Day 7-14 (inclusive)
Visit 3	Test of Cure	Day 21 to 30 (inclusive)

It is expected that approximately 738 subjects will be enrolled in this study and randomized into one of three treatment groups in a 1:1:1 ratio (246 subjects/group). One of three study treatments (metronidazole 0.75% vaginal gel [GDC-229; test article], marketed metronidazole 0.75% vaginal gel [Oceanside Pharmaceuticals], or matched placebo [i.e., GDC-229 vehicle]) will be administrated intravaginally once daily at bedtime for 5 consecutive days.

3.2 Study Design Rationale

The study design outlined in this protocol is primarily based on the April 2013 Food & Drug Administration (FDA) draft guidance for the development of generic metronidazole vaginal gel, 0.75%, equivalent to the reference listed drug Metrogel-Vaginal (NDA 020208). This guidance describes the eligibility criteria for subjects (including Amsel's criteria, which are defined in inclusion criteria; Section 3.3.1), microbiological confirmation of disease, efficacy endpoints, safety considerations, and recommendations for statistical analyses. A placebo arm is included to demonstrate adequate study sensitivity. The dose selection and dosing regimen is based on the FDA approved dose.

Safety considerations specific to the use of metronidazole are described in Section 8.2.

3.3 Selection of Subjects

Approximately 738 generally healthy adult female subjects with a diagnosis of BV based on all four Amsel's criteria will be recruited from approximately 40 research centers in the United States (US). Specific entry criteria are detailed in Section 3.3.1 and Section 3.3.2.

3.3.1 Inclusion Criteria

Subjects meeting all of the following criteria at Entry Visit (Visit 1) may be considered for study participation:

1. Non-pregnant female aged ≥ 18 years who is in good general health
2. Diagnosis of BV, defined as presence of all of the following:
    a. Clinical diagnosis of BV (e.g., off-white [milky or gray], thin homogeneous discharge with minimal or absent pruritus and inflammation of the vulva and vagina); AND
    b. Saline wet mount of vaginal discharge demonstrating the proportion of clue cells to be ≥ 20% of the total epithelial cells; AND
    c. Vaginal secretion pH > 4.5, using pH paper that measures from 4.0 to 6.0; AND
    d. Positive (fish odor) "whiff test" after addition of a drop of 10% potassium hydroxide (KOH) to vaginal discharge.
3. Willing to refrain from vaginal sexual intercourse on Days 1 to 7 (i.e., during treatment and for two post-treatment days) and for 48 hours prior to Visits 2 and 3.
4. Willing to refrain from using any intravaginal product (e.g., spermicide, tampon, douche, feminine deodorant spray, diaphragm, vaginal ring birth control, or condom with spermicide or insertion into the vagina of any drug or non-drug product during treatment), other than study treatment for the duration of the trial.
5. Subjects of childbearing potential who have a negative urine pregnancy test at the Entry Visit (Visit 1) and agree to use an acceptable form of birth control throughout the study. Acceptable forms of birth control include oral contraceptives (the pill), intrauterine devices (IUDs), contraceptive implants under the skin, patches or injections, and condoms without spermicide. Oral or transdermal hormonal contraceptives must be in use for one full cycle (e.g., four to eight weeks) prior to test article application. Injectable or implanted contraceptives (e.g., Depo-Provera, Nexplanon, or hormonal IUD) must be injected/inserted at least seven days prior to test article application. Subjects who are not of childbearing potential, as defined below, must also have a negative urine pregnancy test prior to randomization:
    a. Postmenopausal for at least one year prior to the Entry Visit (Visit 1) (defined as ≥ 50 years of age and amenorrheic for > one continuous year) or
    b. Surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) at least 6 months before first dose or
    c. Non-surgical permanent sterilization (e.g., Essure® procedure) procedure at least 3 months prior to first dose.
6. The subject is willing to refrain from alcohol intake on study Days 1 to 6 (i.e., during treatment through first post-treatment day).
7. Able to understand and willing to sign the informed consent form (ICF) and able to comply with the requirements of the protocol.

3.3.2 Exclusion Criteria

Subjects meeting any of the following criteria at Screening (unless otherwise specified) will be excluded:

1. Known current or recent history (i.e., within the past two years prior to the Entry Visit) of alcohol or substance abuse.
2. Experienced a clinically significant medical event within 90 days prior to the Entry Visit (e.g., stroke, myocardial infarction, surgery).
3. Abnormal pap or high risk human papillomavirus (HPV) within the last three months requiring colposcopic evaluation or treatment (e.g., Cryotherapy, loop electrosurgical excision procedure [LEEP], or conization of the cervix).
4. History or presence of clinically significant central nervous system (CNS), cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, gynecologic, dermatologic, neurologic, oncologic, or psychiatric disease, or any other condition that, in the opinion of the Investigator, would jeopardize the safety of the subject or the validity of the study results.
5. Pregnant, lactating, or planning to become pregnant or breastfeed during the study period.
6. Menstruating when diagnosis of BV is determined at the Entry Visit (Visit 1).
7. Primary or secondary immunodeficiency.
8. History of severe liver disease.
9. History of CNS-related disorders.
10. Evidence of any vulvovaginitis at screening other than BV (e.g., vulvovaginal candidiasis, *Trichomonas vaginalis, Chlamydia trachomatis, Neisseria gonorrhoeae, active* herpes simplex, or active HPV).
11. At the Entry Visit, the subject is receiving any antibacterial therapy unrelated to BV.
12. Subject has received vaginal therapy within two weeks prior to the Entry Visit, or plans to receive vaginal therapy for the duration of the trial.
13. Subject is or will be undergoing treatment for cervical intraepithelial neoplasia (CIN) or cervical carcinoma.
14. History of hypersensitivity or allergy to metronidazole, parabens, other nitroimidazole derivatives, or other ingredients of the GDC-229 (metronidazole 0.75% vaginal gel), metronidazole 0.75% vaginal gel (Oceanside Pharmaceuticals), or vehicle gel.
15. Use within 2 weeks prior to the Entry Visit of 1) disulfiram, 2) lithium, 3) topical or systemic antibiotics, or 4) topical or systemic antifungals.
16. Use of spermicides, tampons, douches, diaphragms, condoms or other intravaginal product within 48 hours prior to dosing on study Day 1.
17. Current use of anticoagulation therapy or cimetidine.
18. Participating in a clinical trial involving an investigational product within the 30 days prior to the Entry Visit (Visit 1) or is planning to participate in another clinical trial during this study.

3.4 Withdrawal of Subjects

Subjects may withdraw from the study at any time or be withdrawn from the study at the discretion of the investigator should any untoward effects occur. In addition, a subject may be withdrawn by the investigator or the sponsor if she deviated from the protocol or for other safety reasons.

Subjects withdrawing from the study will not be replaced, regardless of the reason for discontinuation. All reasonable efforts should be made to contact the subject if she decides to discontinue study treatment.

The procedures noted in the Schedule of Assessments (Table 3) should be performed for the Early Termination Visit, whenever it occurs. A subject will be considered to have completed the study after completing the Test of Cure Visit (Visit 3). If a subject is discontinued at any time after entering the study, the investigator will make every effort to see the subject and complete the early discontinuation assessments as shown in Schedule of Assessments (Table 3) and Section 5.4.

A termination electronic case report form (eCRF) page should be included for each subject who receives study medication, whether or not the subject completes the study. The reason for any early discontinuation should be indicated on the form. The primary reason for a subject withdrawing prematurely should be selected from the list provided in Section 6.2.

3.5 Study Treatments

3.5.1 Method of Assigning Subjects to Treatments

Subjects will be assigned a unique subject identification number during Screening. Following completion of the screening procedures, eligible subjects will be randomized in a blinded manner to one of three treatment groups in a 1:1:1 ratio. It is anticipated that approximately 246 subjects will be randomized to each treatment. The identity and description of study drugs are described in the subsections that follow.

3.5.2 Identity of Study Drug and Treatments Administered

All drug supplies will be provided by the Sponsor. Basic information about the study drug supplies is provided in Table 2.

Table 2 Details on Study Treatments

Characteristic	Treatment		
	GDC-229	**Metronidazole 0.75% Vaginal Gel**	**Vehicle Gel**
Trade Name	Not applicable	Metronidazole Vaginal Gel, 0.75%	Not applicable
Manufactured for	Gage Development Company, LLC, [redacted]	Oceanside Pharmaceuticals, a division of Valeant Pharmaceuticals North America LLC, Bridgewater, NJ 08807	Gage Development Company, LLC, [redacted]
Dose of active ingredient	37.5 mg metronidazole	37.5 mg metronidazole	N/A
Inactive ingredients	Purified Water, Carbomer 934P, Edetate Disodium, Methylparaben, Propylparaben, Propylene Glycol, Sodium Hydroxide	Purified Water, Carbomer 934P, Edetate Disodium, Methylparaben, Propylparaben, Propylene Glycol, Sodium Hydroxide	Purified water, Carbomer 934P, Edetate Disodium, Methylparaben, Propylparaben, Propylene Glycol, Sodium Hydroxide, FD&C Yellow No. 5
Route	Intravaginal	Intravaginal	Intravaginal
Formulation	Gel	Gel	Gel
Total daily dose	37.5 mg	37.5 mg	N/A
Total dose administered in the study	Approximately 187.5 mg	Approximately 187.5 mg	N/A

Study drug will be dispensed to eligible subjects at the Entry Visit (Visit 1). The investigator will instruct the subjects to fill applicator and self-administer study drug intravaginally once daily at bedtime for 5 consecutive days. Treatment should begin the same night as the Entry Visit (Visit 1). Each applicator, once filled with the 5 gram dose, will contain either 37.5 mg of metronidazole (test or reference product) or placebo. Each applicator is for single use only. All treatments will have identical packaging so that subjects and investigators will remain blinded to the treatments.

3.5.3 Contraindications, Warnings, and Precautions

Contraindications, warnings, and precautions are specified below as noted from the Metronidazole Vaginal Gel 0.75% Label, dated 4/2015.

3.5.3.1 Contraindications

Metronidazole vaginal gel is contraindicated in patients with a prior history of hypersensitivity to metronidazole, parabens, other ingredients of the formulation, or other nitroimidazole derivatives.

3.5.3.2 Warnings

3.5.3.2.1 Convulsive Seizures and Peripheral Neuropathy

Convulsive seizures and peripheral neuropathy, the latter characterized mainly by numbness or paresthesia of an extremity, have been reported in patients treated with oral or intravenous metronidazole. The appearance of abnormal neurologic signs demands the prompt discontinuation of metronidazole vaginal gel therapy. Metronidazole vaginal gel should be administered with caution to patients with CNS diseases.

3.5.3.2.2 Psychotic Reactions

Psychotic reactions have been reported in alcoholic patients who were using oral metronidazole and disulfiram concurrently. Metronidazole vaginal gel should not be administered to patients who have taken disulfiram within the last two weeks.

3.5.3.3 Precautions

Metronidazole vaginal gel results in minimal peak serum levels and systemic exposure (AUCs) of metronidazole compared to 500 mg oral metronidazole dosing. Although these lower levels of exposure are less likely to produce the common reactions seen with oral metronidazole, the possibility of these and other reactions cannot be excluded presently. Data from well-controlled trials directly comparing metronidazole administered orally to metronidazole administered vaginally are not available.

3.5.3.3.1 General

Patients with severe hepatic disease metabolize metronidazole slowly. This results in the accumulation of metronidazole and its metabolites in the plasma. Accordingly, for such patients, metronidazole vaginal gel should be administered cautiously.

Known or previously unrecognized vaginal candidiasis may present more prominent symptoms during therapy with metronidazole vaginal gel. Approximately 6-10% of patients treated with metronidazole vaginal gel developed symptomatic Candida vaginitis during or immediately after therapy.

Disulfiram-like reaction to alcohol has been reported with oral metronidazole, thus the possibility of such a reaction occurring while on metronidazole vaginal gel therapy cannot be excluded.

Metronidazole vaginal gel contains ingredients that may cause burning and irritation of the eye. In the event of accidental contact with the eye, rinse the eye with copious amounts of cool tap water.

3.5.3.3.1.1 Information for the Patient:

The patient should be cautioned about drinking alcohol while being treated with metronidazole vaginal gel. While blood levels are significantly lower with Metronidazole Vaginal Gel than with usual doses of oral metronidazole, a possible interaction with alcohol cannot be excluded.

[redacted]

The patient should be instructed not to engage in vaginal intercourse during treatment with this product (in addition, the protocol requires that the subject not engage in vaginal intercourse for the two days following treatment or for 48 hours prior to Visits 2 and 3).

3.5.3.3.1.2 Drug Interactions

Oral metronidazole has been reported to potentiate the anticoagulant effect of warfarin and other coumarin anticoagulants, resulting in a prolongation of prothrombin time. This possible drug interaction should be considered when metronidazole vaginal gel is prescribed for patients on this type of anticoagulant therapy.

In patients stabilized on relatively high doses of lithium, short-term oral metronidazole therapy has been associated with elevation of serum lithium levels and, in a few cases, signs of lithium toxicity.

Use of cimetidine with oral metronidazole may prolong the half-life and decrease plasma clearance of metronidazole.

3.5.3.3.1.3 Drug/Laboratory Test Interactions

Metronidazole may interfere with certain types of determinations of serum chemistry values, such as aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), lactate dehydrogenase (LDH), triglycerides, and glucose hexokinase. Values of zero may be observed. All of the assays in which interference has been reported involve enzymatic coupling of the assay to oxidation-reduction of nicotinamide-adenine dinucleotides (NAD + NADH). Interference is due to the similarity in absorbance peaks of NADH (340 nm) and metronidazole (322 nm) at pH 7.

3.5.3.3.1.4 Carcinogenesis, Mutagenesis, Impairment of Fertility

Metronidazole has shown evidence of carcinogenic activity in a number of studies involving chronic oral administration in mice and rats. Prominent among the effects in the mouse was the promotion of pulmonary tumorigenesis. This has been observed in all six reported studies in that species, including one study in which the animals were dosed on an intermittent schedule (administration during every fourth week only). At very high dose levels (approximately 500 mg/kg/day), there was a statistically significant increase in the incidence of malignant liver tumors in males. Also, the published results of one of the mouse studies indicate an increase in the incidence of malignant lymphomas as well as pulmonary neoplasms associated with lifetime feeding of the drug. All these effects are statistically significant. Several long-term oral dosing studies in the rat have been completed. There were statistically significant increases in the incidence of various neoplasms, particularly in mammary and hepatic tumors, among female rats administered metronidazole over those noted in the concurrent female control groups. Two lifetime tumorigenicity studies in hamsters have been performed and reported to be negative.

These studies have not been conducted with 0.75% metronidazole vaginal gel, which would result in significantly lower systemic blood levels than those obtained with oral formulations.

Although metronidazole has shown mutagenic activity in a number of in vitro assay systems, studies in mammals (in vivo) have failed to demonstrate a potential for genetic damage.

Fertility studies have been performed in mice up to six times the recommended human oral dose (based on mg/m^2) and have revealed no evidence of impaired fertility.

3.5.3.3.1.5 Pregnancy: Teratogenic Effects

Pregnancy Category B

There has been no experience to date with the use of Metronidazole Vaginal Gel in pregnant patients.

Metronidazole crosses the placental barrier and enters the fetal circulation rapidly. No fetotoxicity or teratogenicity was observed when metronidazole was administered orally to pregnant mice at six times the recommended human dose (based on mg/m^2); however, in a single small study where the drug was administered intraperitoneally, some intrauterine deaths were observed. The relationship of these findings to the drug is unknown. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, and because metronidazole is a carcinogen in rodents, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Specific studies of metronidazole levels in human milk following intravaginally administered metronidazole have not been performed. However, metronidazole is secreted in human milk in concentrations similar to those found in plasma following oral administration of metronidazole. Because of the potential for tumorigenicity shown for metronidazole in mouse and rat studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in children have not been established.

3.5.3.4 Adverse Events

3.5.3.4.1 Clinical Trials

There were no deaths or serious adverse events related to drug therapy in clinical trials involving 800 non-pregnant women who received metronidazole vaginal gel.

In a randomized, single-blind clinical trial of 505 non-pregnant women who received metronidazole vaginal gel once or twice a day, 2 patients (one from each regimen) discontinued therapy early due to drug-related adverse events. One patient discontinued drug because of moderate abdominal cramping and loose stools, while the other patient discontinued drug because of mild vaginal burning. These symptoms resolved after discontinuation of drug.

Medical events judged to be related, probably related, or possibly related to administration of metronidazole vaginal gel once or twice a day were reported for 195/505 (39%) patients. The incidence of individual adverse reactions were not significantly different between the two regimens.

Unless percentages are otherwise stipulated, the incidence of individual adverse reactions listed below was less than 1%:

- Reproductive: Vaginal discharge (12%), Symptomatic Candida cervicitis/vaginitis (10%), Vulva/vaginal irritative symptoms (9%), Pelvic discomfort (3%)
- Gastrointestinal: Gastrointestinal discomfort (7%), Nausea and/or vomiting (4%), Unusual taste (2%), Diarrhea/loose stools (1%), Decreased appetite (1%), Abdominal bloating/gas; thirsty, dry mouth
- Neurologic: Headache (5%), Dizziness (2%), Depression
- Dermatologic: Generalized itching or rash
- Other: Unspecified cramping (1%), Fatigue, Darkened urine

In previous clinical trials submitted for approved labeling of Metronidazole Vaginal Gel the following was also reported:

- Laboratory: Increased/decreased white blood cell counts (1.7%)

3.5.4 Drug Packaging and Labeling

All packaging and labeling of study medication will be prepared in accordance with ICH E6 Section 5.1.3. Each subject package will consist of five empty applicators and metronidazole 0.75% vaginal gel (GDC-229; test article), or metronidazole 0.75% vaginal gel (Oceanside Pharmaceuticals), or vehicle (placebo) and will be labeled with identification that maintains the blind, randomization number, and the FDA-required caution statement for an investigational new drug. The investigator or designee will record the subject identification and date dispensed on the packaging and will record the randomization information in the subject's source documentation. Instructions for use will be provided to the subject.

3.5.5 Drug Storage

Study medication will be stored per the reference product label at room temperature (15 to 30°C/59-86° F) in a secure storage area at the study site. Study medication will only be accessible only to designated study personnel.

3.5.6 Drug Disposal/Return

Study medication, used and unused, with the exception of retention samples will be returned to the depot per instructions provided to the sites after accountability by the clinical monitor has been performed.

3.5.7 Retention Samples

Each site will be required to randomly select reserve samples from the shipment of test articles. Instructions regarding the number of kits to select and how to document the kits selected as reserve samples will be included in the shipment. Each site will then store the reserve samples under conditions consistent with the approved product labeling in an area segregated from the area where testing is conducted, with access limited to authorized personnel only. In accordance with 21 CFR 320.38 and 21 CFR 320.63, each reserve sample must be retained for a period of at least five years following the date on which the application is approved, or, if the application is not approved, at least five years following the date of completion of this study.

3.5.8 Blinding and Unblinding

This is a double-blind study. Every effort will be made to ensure that the investigator and subjects will be blinded to study treatment for the duration of the study.

If the treatment assignment must be revealed for the safety of the subject or to treat an AE, the investigator will contact the medical monitor. A decision to break the blind must be reached by the medical monitor or designee and the investigator.

The investigator or designee may break the blind independent of the medical monitor only if it is considered an emergency by the investigator. If this occurs, the medical monitor and the sponsor must be notified within 48 hours of breaking the blind. The event requiring breaking the blind must be documented in the eCRF, including the date the blind was broken. In addition, the subject will be discontinued from further study drug administration in this study.

3.5.9 Treatment Compliance

Subjects will be required to return unused study medication and unused applicators and subject compliance information will be captured. The sites will record return of study medication and supplies in the subject source documentation and eCRF and will retain all returned tubes and unused applicators for verification by the clinical monitor prior to return of study medication to the depot. Compliance will be assessed based on the subject's verbal agreement on doses given and absence of unused applicators.

3.5.10 Prior and Concomitant Medications

Certain medications may interfere with study medication and will not be allowed during the course of the study.

The following may not be used within two weeks of study Entry Visit (Visit 1) or during the study:

- Disulfiram
- Lithium
- Topical or systemic antibiotics
- Topical or systemic antifungals

In addition to the above, the following may not be used at any time during the study:

- Anticoagulation therapy
- Cimetidine
- Any intravaginal products including: Spermicides (including condoms with spermicide lubricants), douches, tampon, feminine deodorant spray, diaphragm, or vaginal ring birth control
- Vaginal therapy
- Any other investigational medication

A subject with recent use of an exclusionary medication may participate if she has discontinued use of the drug for the number of days prior to the screening visit as specified in the

inclusion/exclusion criteria list. The reason for discontinuation of the medication must not be solely for participation in the study. All concomitant treatments will be recorded in the subject's medical records, including the name of the drug, start and stop dates, and reason for use. Other prescriptions for the treatment of intercurrent medical conditions should be discussed with the medical monitor and recorded.

4 STUDY PROCEDURES

Refer to the Schedule of Assessments (Table 3) for timing of assessments. Additional details are provided in the sections that follow. Results of all procedures and assessments will be recorded in the subject's source documentation and Electronic Data Capture (EDC) system.

4.1 Informed Consent

Each subject must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the subject's standard of care.

4.2 Subject Demographics, Height, and Weight

The date of birth, race, ethnicity, and sex of the subject are to be recorded at the Entry Visit (Visit 1). Height will be measured only at the Entry Visit (Visit 1). Weight will be measured at Visits 1 and 3.

4.3 Medical and Gynecological History

At the Entry Visit (Visit 1), a complete medical and gynecological history will be compiled for each subject, including prior and concomitant illnesses. The following information will be recorded: acute and chronic history of medical and gynecological conditions, smoking, illicit drug and alcohol use history, menstrual cycle history, sexual history including history of sexually-transmitted infections (STIs) including BV, current sexual activity, previous/current contraceptive use, and pregnancy history.

4.4 Physical and Pelvic Examination

A physical examination will be completed at Visits 1 and 3 and pelvic examinations will be completed at each visit.

4.5 Vital Signs

Vital sign measurements will be completed at each visit. Vital sign measurements include sitting (after 5 to 10 minutes in this position) measurements of diastolic and systolic blood pressure, heart rate, respiratory rate, and oral temperature.

4.6 Concomitant Medications and Procedures

Medications used by the subject will be recorded at each visit.

See Section 3.5.10 for a list of medications prohibited during the study.

4.7 Adverse Events (AEs)

Monitoring of AEs will be completed at all visits. Briefly, any untoward events reported by the subject or observed by the study staff following the first dose of study medication are to be recorded as AEs. Any untoward events that occur prior to this time are recorded in the medical history page of the eCRF. Refer to Section 8 for details regarding definitions, documentation, and reports of AEs and serious adverse events (SAEs).

4.7.1 Local Site Reactions

Investigator or designee will assess treatment area and rate on a scale of 0 = absent, 1 = mild (slight, barely perceptible), 2 = moderate (distinct presence), and 3 = severe (marked, intense) the following at Visits 2 and 3:

- Erythema
- Petechiae
- Erosion/ulceration
- Edema

The subject will be queried by the Investigator or designee for presence of the following and, if present, the subject will be asked to rate as described above:

- Burning/stinging
- Pain
- Pruritus (itching)

Local site reactions will be collected independently of AEs and will include any reaction that occurs within the treatment area. Local site reactions that require medical intervention (e.g., prescription medication) or extend beyond the treatment area should be documented as an AE.

4.8 Clinical Laboratory Evaluations

4.8.1 Urine Drug Screening

At the Entry Visit (Visit 1), urine drug screening will be completed.

4.8.2 Pregnancy Testing

Pregnancy testing via urine hCG testing (serum hCG testing will be done only if deemed necessary by the PI) will be performed for each subject, regardless of childbearing potential, at each visit. Additional pregnancy testing may also be performed if there is any suspicion or clinical concern that a woman might be pregnant at any time during the study.

4.8.3 Screening for Sexually Transmitted Infections

At the Entry Visit (Visit 1) pelvic examination, a sample will be collected for assessment of sexually transmitted infections (STI) for *Chlamydia trachomatis, Neisseria gonorrhoeae*.

4.8.4 Microbiological Sample

A wet smear microbiological sample will be collected at each visit in order to determine if Amsel's criteria are met/or resolved. Evidence of any vulvovaginitis other than BV. (e.g., vulvovaginal candidiasis, *Trichomonas vaginalis, Chlamydia trachomatis, Neisseria gonorrhoeae, active* Herpes simplex, or active HPV will also be ruled out in order to ensure study eligibility. In addition, a specimen for Gram stain will be collected at Visits 1 and 3. Details for collection, preparation, and evaluation of microbiological samples by the central lab will be provided in the study laboratory manual.

5 SCHEDULE OF ASSESSMENTS AND STUDY VISIT PROCEDURES

The study will include three visits:

- Entry Visit (Visit 1)
- Post-Treatment Assessment (Visit 2)
- Test of Cure (Visit 3)

Refer to Table 3, Schedule of Assessments.

5.1 Entry Visit (Visit 1)

During the screening portion of the Entry Visit (Visit 1), the following should be completed:

- Obtain written informed consent.
- Perform urine pregnancy test.
- Review and confirm inclusion and exclusion criteria.
- Obtain demographic data.
- Collect medical and gynecological history, including sexual history, information on the subject's menstrual cycle, and history of STIs.
- Obtain vital signs after sitting for 5 – 10 minutes (Section 4.5).
- Record height and weight.
- Record current medications and prior medications taken within three months prior to the start of screening, in addition to the indication for the medication and reasons for discontinuing medication.
- Perform complete physical and pelvic examination including a vaginal wall inspection (i.e., a naked eye inspection) as well as an examination of the cervix.
- Perform urine drug screening.
- Collect Chlamydia and gonorrhea swab samples for central laboratory analysis.
- Collect a swab sample for central laboratory Nugent's analysis for BV via Gram stain.
- Screen for presence of BV by assessing the subject for presence of the four Amsel's criteria. (Note: The four Amsel's criteria are the only BV diagnostic criteria on which the decision to randomize is made; Nugent's result is not used for randomization decisions). If the results of the Amsel's screening tests are positive and the subject is eligible according to all other inclusion/exclusion criteria, the subject can be randomized to treatment:
  - Clinical diagnosis of BV (e.g., thin, homogeneous off-white [milky or grayish] vaginal discharge associated with minimal or absent pruritus inflammation); AND
  - Saline wet mount of vaginal discharge demonstrating the proportion of clue cells to be ≥ 20% of the total epithelial cells; AND
  - Vaginal secretion pH > 4.5; AND

  - Positive "whiff test" after addition of a drop of 10% KOH to vaginal discharge.
- Assess the saline wet mount for evidence of any vulvovaginitis other than BV. (e.g., vulvovaginal candidiasis, *Trichomonas vaginalis, Chlamydia trachomatis, Neisseria gonorrhoeae,* active herpes simplex, or active HPV) per laboratory manual.
- An overall determination of the subject's eligibility will be made based on the results of the assessments noted above as well as all inclusion and exclusion criteria (see Section 3.3).
- Dispense study medication, explain appropriate application to subjects, and give the subject a copy of the Subject Dosing Instructions for Study Medication (Appendix 2).
- Schedule the subject for Visit 2 and Visit 3 and add the visit dates to page 2 of the Subject Dosing Instructions for Study Medication. Note: The subject should not be menstruating during the five days of study medication administration or be scheduled for Study Visits 2 or 3 when menstruating in order for assessments to be accurate.

5.2 Post-Treatment Assessment (Visit 2)

Visit 2 will occur 7 to 14 days after randomization. During this visit, the following procedures will be performed:

- Obtain vital signs after sitting for 5 – 10 minutes (Section 4.5).
- Perform urine pregnancy test.
- Perform pelvic examination including vaginal wall inspection (a naked eye inspection), examination of the cervix, and Investigator's assessment of local site reactions.
- Record subject-assessed local site reactions (e.g., itching, burning/stinging, localized pain).
- Perform clinical test of response by assessing the subject for presence of these three of the Amsel's criteria:
  - Resolution of the abnormal vaginal discharge characteristic of BV to a normal physiological discharge; AND
  - Negative "whiff test" after addition of a drop of 10% KOH to vaginal discharge; AND
  - Presence of clue cells at <20% of the total epithelial cells on microscopic examination of the saline wet mount.
- Determine if vaginal pH is <4.7, which is part of the assessment of therapeutic cure (defined as clinical cure, vaginal pH <4.7 and bacteriological cure).
- Record concomitant medications taken since the prior visit along with the indications for the medications.
- Study medication remaining in the tube will be returned by subjects, including unused applicators. Verify that the subject inserted the medication according to instructions and for five consecutive days.
- Assess and record AEs.

- Confirm the date of the subject's Visit 3 will still likely occur on a day that the subject is not expecting menstruation. Note: The subject should not be menstruating during the five days of study medication administration or be scheduled for Study Visits 2 or 3 when menstruating in order for assessments to be accurate.

5.3 Test of Cure Visit (Visit 3)

The Test of Cure Visit (Visit 3) will occur 21 to 30 days after Visit 1. This is the last visit of the study. The following will be completed:

- Perform physical examination.
- Obtain vital signs after sitting for 5 – 10 minutes (Section 4.5).
- Measure weight.
- Perform urine pregnancy test.
- Perform pelvic examination including vaginal wall inspection (a naked eye inspection), examination of the cervix, and Investigator's (or designee's) assessment of local site reactions.
- Record subject-assessed local site reactions (e.g., itching, burning/stinging, localized pain).
- Collect a swab sample for central laboratory Nugent's analysis for BV via Gram stain.
- Determine clinical cure of BV by assessing the subject for presence of the following three Amsel's criteria:
  - Resolution of the abnormal vaginal discharge characteristic of BV to a normal physiological discharge; AND
  - Negative "whiff test" after addition of a drop of 10% KOH to vaginal discharge; AND
  - Presence of clue cells at <20% of the total epithelial cells on microscopic examination of the saline wet mount.
- Determine if vaginal pH is <4.7, which is part of the assessment of therapeutic cure (defined as clinical cure, vaginal pH <4.7 and bacteriological cure).
- Record concomitant medications taken since the prior visit along with the indications for the medications.
- Assess and record AEs.

5.4 Early Discontinuation Visit

At any time, if a subject decides to discontinue her participation in the study or is discontinued from the study for any reason, she will be advised to complete Early Termination procedures (i.e., all procedures noted for Visit 3) as an early discontinuation visit. The following will be completed:

- Perform physical examination.
- Obtain vital signs after sitting for 5 - 10 minutes (Section 4.5).
- Measure weight.

- Perform urine pregnancy test.
- Perform pelvic examination including vaginal wall inspection (a naked eye inspection), examination of the cervix, and local site reaction assessments.
- Record subject-assessed local site reactions (e.g., itching, burning/stinging, localized pain).
- Collect a swab sample for central laboratory Nugent's analysis for BV via Gram stain.
- Clinical test of response of BV will be determined by assessing the subject for presence of these three of the Amsel's criteria:
  - Resolution of the abnormal vaginal discharge; AND
  - Negative "whiff test" after addition of a drop of 10% KOH to vaginal discharge; AND
  - Presence of clue cells at <20% of the total epithelial cells on microscopic examination of the saline wet mount.
- Determine if vaginal pH is <4.7, which is part of the assessment of therapeutic cure (defined as clinical cure, vaginal pH <4.7 and bacteriological cure).
- Study medication will be returned by the subject, including any unused applicators (unless previously collected).
- Record concomitant medications taken since the prior visit along with the indications for the medications.
- Assess and record AEs.

5.5 Unscheduled Visit

The investigator may see the subject for an unscheduled visit to manage or assess AEs.

At this visit, the investigator or designee will:

- Assess AEs and local site reactions since the last visit; AEs and local site reactions will be recorded.
- Record any changes in the subject's concomitant medications.
- Confirm the next appointment (to be done at a time the subject does not expect to be menstruating).

5.6 Schedule of Assessments

The schedule of assessments is provided in Table 3.

Table 3 Schedule of Assessments

Visit	**Visit 1**	**Visit 2**	**Visit 3**	
Visit Name	**Entry Visit**	**Post-Treatment Assessment**	**Test of Cure**	**Early Termination[a]**
Study Day(s)	**1**	**7 to 14 days**	**21 to 30**	
Informed consent	X			
Inclusion/exclusion criteria	X			
Demographics	X			
Medical and gynecological history	X			
Physical examination	X		X	X
Pelvic examination	X	X	X	X
Height	X			
Weight	X		X	X
Vital signs (after sitting for 5 - 10 mins)	X	X	X	X
Concomitant medications	X	X	X	X
Randomization[b]	X			
Dispense study medication[c] and dosing instructions	X			
Collect study medication		X		X[d]
Assessment of local site reactions		X	X	X
Adverse events	X	X	X	X
Urine pregnancy test	X	X	X	X
Urine drug screen	X			
Amsel's criteria evaluations:				
-Assessment of vaginal discharge	X	X	X	X
-KOH Whiff Test	X	X	X	X
-Saline Wet Mount	X	X	X	X
-pH	X	X	X	X
Collection of samples for Nugent's score based on Gram stain (send to central laboratory)	X		X	X
Collection of samples for STI assessment[e] (send to central laboratory)	X			

a. At any time a subject decides to discontinue her participation in the study or is discontinued from the study for any other reason, she will be advised to complete the Early Termination procedures.
b. Randomization to occur if the results of the full set of Amsel's criteria are positive.
c. Study medication will be dispensed at Visit 1. The subject will be instructed to self-administer study medication intravaginally once daily at bedtime for 5 consecutive days.
d. Unless collected at previous visit.
e. Central laboratory analysis for *Chlamydia trachomatis* and *Neisseria gonorrhoeae.*

6 END OF STUDY CRITERIA

At the end of each subject's participation in the study, the investigator will complete an End of Study form for all completed and discontinued subjects.

6.1 Completion of the Study

Subjects who complete the 5-day treatment and all of the evaluations at the Assessment of Clinical Cure Visit (Visit 3) will be considered to have completed the study.

6.2 Subject Discontinuation

A subject may be withdrawn from the study prior to completion for any of the following reasons:

- AEs
- Abnormal laboratory values
- Death
- Lack of efficacy
- Lost to follow-up
- Noncompliance with study drug
- Physician decision
- Pregnancy (if applicable)
- Protocol deviation
- Study terminated by Sponsor
- Withdrawal by subject; NOTE: if the subject decides to withdraw from the study due to an AE then it should be classified as withdrawal due to an AE.
- Other (e.g., any reason that may affect the outcome of the study or safety of subjects)

If a subject withdraws prematurely for any reason, the site should make every effort to have the subject return for her next scheduled visit to perform all required visit activities and to collect and reconcile all test article. If the subject is discontinued prior to the Assessment of Clinical Cure Visit (Visit 3; Day 21 to 30), the site should complete the End of Study eCRFs during the last visit that the subject will complete. Subjects who withdraw prematurely will not be replaced. When a subject is withdrawn from the study for a treatment-related AE (i.e., as defined in Section 8.1.2), when possible, the subject should be followed until resolution or stabilization of the AE. If a subject is discontinued from the study due to pregnancy, the pregnancy and its outcome should be followed (see Section 8.1.5).

6.3 Study Termination

The study may be terminated by the Sponsor. If, in the opinion of the investigator, clinical observations made during the study suggest that it may be unwise to continue, he or she may discontinue his or her participation in the study.

If an investigator decides to terminate his or her participation, a written statement fully documenting the reasons for this action will be submitted to the Sponsor by the investigator within five working days.

In the event that the Sponsor chooses to discontinue or terminate the study, appropriate notification will be given to the investigator.

7 EVALUATIONS

7.1 Efficacy Parameters

The primary efficacy endpoint (Clinical Cure) is the resolution of the following three abnormal BV signs included in Amsel's criteria: return to normal physiological vaginal discharge as determined by the investigator, negative whiff test, and the presence of clue cells at <20% of the total epithelial cells on microscopic examination of the saline wet mount.

The supportive secondary efficacy endpoints are the Bacteriological Cure and the Therapeutic Cure. The bacteriological cure is defined as Nugent's score <4 (via Gram stain central laboratory analysis). A Nugent score ≥4 is considered abnormal and represents an imbalance in vaginal flora that permits BV to manifest (Nugent 1991). Subjects who are responders are expected to achieve a normal Nugent score (i.e., 0 to 3) following treatment.

Therapeutic cure is defined as having achieved clinical cure, vaginal pH of <4.7, and bacteriological cure (i.e., Nugent score of < 4 at Visit 3).

7.2 Safety Evaluation

Each subject's health status will be monitored carefully throughout the study. Baseline data collected will consist of the medical and gynecological history and physical examination findings, including pelvic examinations (to include STI screening for Chlamydia and gonorrhea).

Vital signs include oral temperature, sitting blood pressure, heart rate, and respiratory rate. Blood pressure will be collected after sitting for 5 to 10 minutes and should be taken from the same arm at each visit.

Weight will be recorded at the Entry Visit (Visit 1) and the Assessment of Continued Clinical Cure Visit (Visit 3).

Subjects who withdraw from the study will have all safety assessments repeated except for urine drug and STI testing, if the subject allows.

At every visit or contact, subjects will be questioned about how they have been feeling and any symptoms they have experienced. Interviews with subjects will include a review of any AE reported in order to obtain as much information as possible (e.g., onset date, duration, intensity). The AEs will be recorded at each visit in the medical records and the eCRF. See Section 8.1 for AE definitions and criteria, including assessments for intensity and relatedness. In addition, local site reactions based on investigator examination and subject self-report will assessed at Visits 2 and 3.

The principal investigator (or designated medical designee) will review each AE, assess severity and causality and will report it in accordance with established procedures (see Section 8.1.1.4).

There will be strict adherence to SAE reporting (see Section 8.1.3.2).

7.3 Appropriateness of Measurements

As stated in Section 3.2, the study design relied heavily on the recommendations provided in FDA draft guidances.

8 SAFETY

The primary method of assessing safety will be collection and analysis of AEs. AEs and SAEs will be carefully monitored throughout this study.

8.1 Adverse Events and Serious Adverse Events

8.1.1 Definitions and Criteria

8.1.1.1 Adverse Events (AEs)

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered 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 medicinal product.

Suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. “Reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

An adverse reaction is any AE 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. For the purposes of prescription drug labeling, the term adverse reaction is defined to mean “an undesirable effect, reasonably associated with the use of a drug that may occur as part of the pharmacological action or may be unpredictable in its occurrence. This definition does not include all AEs observed during use of a drug, only those AEs for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the AE”.

An AE or suspected adverse reaction is considered “unexpected” if it is not listed in the RLD package insert or is not listed at the specificity or severity that has been observed. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the RLD package insert referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the RLD package insert listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the RLD package insert as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Timely and complete reporting of all AEs assists [redacted] in identifying any untoward medical occurrence, thereby allowing:

1) protection of the safety of study subjects;

2) a greater understanding of the overall safety profile of the test article;

3) recognition of dose-related test article toxicity;

4) appropriate modification of study protocols;

5) improvements in study design or procedures; and

6) adherence to worldwide regulatory requirements.

Any adverse change from the study participant's baseline condition that occurs following the first administration of study product is an AE. This includes the occurrence of a new AE or the worsening of a baseline condition, whether or not considered related to the study product. AEs include but are not limited to: adverse changes in the general condition of the study participant; signs and symptoms noted by the study participant or her caregiver; concomitant disease with onset or increased severity after the start of study product administration and clinically meaningful adverse changes in laboratory safety parameters occurring after the start of study product administration. Day-to-day fluctuations in pre-existing conditions that represent a clinically significant change in the participant's status should be reported as AEs.

8.1.1.2 Local Site Reactions

Investigator or designee will assess treatment area and rate on a scale of 0 = absent, 1 = mild (slight, barely perceptible), 2 = moderate (distinct presence), and 3 = severe (marked, intense) the following at Visits 2 and 3:

- Erythema
- Petechiae
- Erosion/ulceration
- Edema

The subject will be queried by the Investigator or designee for presence of the following and, if present, the subject will be asked to rate as described above:

- Burning/stinging
- Pain
- Pruritus (itching)

Local site reactions will be collected independently of AEs and will include any reaction that occurs within the treatment area. Local site reactions that require medical intervention (e.g., prescription medication) or extend beyond the treatment area should be documented as an AE.

8.1.1.3 Serious Adverse Events (SAEs)

An AE is considered "serious" if, in the view of either the investigator or sponsor, it meets the criteria for any of the following outcomes:

1. Death.
2. Life-threatening. This term refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization. In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.

Complications that occur during hospitalization are AEs or SAEs as defined above. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment or procedures of a pre-existing condition that did not worsen from baseline is not considered an AE.

4. Results in persistent or significant disability/incapacity. The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
5. Is a congenital anomaly/birth defect.

Medical or scientific judgment should be exercised in deciding whether (expedited) reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These medically important events should also be considered SAEs. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that result in hospitalizations; or development of drug dependency or drug abuse.

In addition, cancer and drug overdose are included in [redacted] classification of an SAE.

8.1.1.4 Unexpected Adverse Drug Reactions

All AEs should be reported, whether or not they are considered to be related to the treatment. The report of AEs should include date of onset, description of the AE, severity, relation to study medication, action taken, outcome, and date of resolution. This information is needed to determine if the incidence and severity of adverse reactions is different between the test articles.

8.1.2 Assessing Intensity and Relationship of Adverse Events

8.1.2.1 Intensity

The intensity of the AE will be characterized as mild, moderate, or severe using the following criteria:

- Mild: Subject was aware of the event, but was still able to do all activities
- Moderate: Subject had to discontinue some activities due to the event
- Severe: Subject was incapacitated by the event and unable to perform normal activities

8.1.2.2 Relationship to Study Drug

The site investigator is responsible for assessing the relationship between the AE and the study product. The investigator must determine whether there is a reasonable possibility that the study product caused or contributed to an AE. The relationship assessment, based on clinical judgment, often relies on the following:

- A temporal relationship between the event and administration of study product

- A plausible biological mechanism for the study product to cause the AE
- Another possible etiology of the AE
- Previous report of similar AEs associated with the study product or other agents in the same class

The terms used to assess the relationship of an AE to study drug are included in Table 4.

Table 4 Assessment of Causality and Relationship to Study Drug

Causality Assessment	Criteria for Assessment (note that re-challenge will not be done in this study)
Related	The experience occurs immediately following study drug administration, related pharmacologically (not related to underlying condition/concurrent disease or other drugs or chemicals) and follows a known response pattern to the study drug.
Possibly Related	The experience follows a reasonable temporal sequence from the time of drug administration and/or follows a known response pattern to the trial drug but could have been produced by other factors such as the participant's clinical state, therapeutic intervention or concomitant therapy.
Not Related	There is not a reasonable possibility that the AE is related to the study product; when an AE is assessed as not related to the study product, an alternative etiology, diagnosis or explanation for the AE should be documented. If new information becomes available, the relationship of any AE should be reviewed again and updated, as required.

8.1.3 Reporting Procedures and Requirements for Adverse Events

8.1.3.1 Study Reporting Period for Adverse Events

At every visit or contact, study staff will ask each participant how she felt since her last visit and indirectly ask if she has experienced any AEs.

The reporting period for AEs is the period immediately following the signing of the ICF through 30 days after last use of study product.

For the purposes of study analysis, if a non-serious AE has not resolved at the end of the study-reporting period it will be reported as still ongoing in the EDC system. However, the investigator must make every reasonable effort to follow the event to resolution or stabilization and report to [redacted].

SAEs must be followed until resolution. Resolution of an SAE is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

8.1.3.2 Recording of Adverse Events

AEs will be reported in the EDC system using a recognized medical term or diagnosis that accurately reflects the event. Information recorded in the EDC system must be substantiated in the source documents. All AEs must be recorded in the participant's source documents and must include the following information (when applicable):

- Specific condition or event.
- Possible etiologies and whether the event meets criteria as an SAE and therefore requires immediate notification to the sponsor. (See Section 8.1.1.3 for the definition of SAEs.)
- Indication of whether the condition was preexisting prior to study entry or not and if yes, whether it has worsened in severity or frequency, in which case it is reported as an AE. Conditions present prior to study entry that do not worsen in severity are not considered AEs.
- Date of occurrence.
- Date of resolution. If the event has not resolved at the end of the study-reporting period, it will be reported as still present in the EDC system.
- AEs that change in intensity are recorded at the most severe intensity level that is reported by the participant.
- Relationship to study product as evaluated by the investigator (causality assessment).
- Action taken with the study product per the investigator medical judgment (study product interrupted, discontinued or none) and outcome.
- Seriousness: An SAE, in accordance with 21 CFR 312.32 (a), means "any adverse event occurring at any dose that results in any of the following outcomes: death, a life threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization or development of drug dependency or drug abuse." In addition, cancer and drug overdose are included in [redacted] classification of an SAE.

8.1.3.3 Notification to Sponsor of Serious Adverse Events

All SAEs will be reported promptly in accordance with the FDA regulations and recorded on the appropriate forms.

WHEN ANY SAE, REGARDLESS OF RELATIONSHIP TO THE STUDY PRODUCT, IS ENCOUNTERED DURING THIS CLINICAL TRIAL AT AN INVESTIGATOR'S SITE, THE INVESTIGATOR, IN ACCORDANCE WITH 21 CFR 312.64(b), MUST NOTIFY [redacted] WITHIN 24 HOURS OF IDENTIFICATION/AWARENESS OF THE SAE BY REPORTING THE EVENT VIA THE EDC SYSTEM AND VIA THE SAE REPORTING FORM FOR THIS STUDY. SAE SUBMISSION SHOULD BE COMPLETED FOR ANY SAE THAT IS EXPERIENCED AFTER THE SUBJECT HAS SIGNED THE ICF, EVEN IF INVESTIGATIONAL PRODUCT HAS NOT YET BE ADMINISTERED.

The investigator should complete the AE eCRF within the EDC system and mark the AE as serious which will send the appropriate notifications to the Medical Monitor as well as the appropriate [redacted] staff. The clinical investigator is to also send an SAE Report Form by email to [redacted]

All SAEs whether or not thought related to the study drug, must be reported by the Study Investigator (by telephone, fax or email) to [redacted] within 24 hours of the investigator becoming aware of the event.

SAE reports should be sent to:

[redacted]

The investigator or responsible site staff will enter all AEs into the eCRF as delineated above. AEs that are assessed as serious also require the completion of a separate SAE report. Following receipt of the SAE report, the SAE reporting contact will review.

Additional supporting documentation for SAEs (i.e. hospital discharge summary, lab report, etc.) which should be provided whenever possible (with participant name redacted) to verify the medical diagnosis includes hospital discharge summaries and death certificates/autopsy reports (where applicable), surgical procedure summaries, histology reports, and imaging reports should be uploaded to the study document repository or [redacted] EDC page as outlined in the Study Procedures Manual within three days of receipt at the site. [redacted] will ensure appropriate copies of supporting document are provided to the Medical Monitor.

NOTE: Investigators should not wait to collect the additional information needed to fully document the event before submission of an SAE.

The SAE report will be sent immediately to the Sponsor for assessment and report to health authorities where appropriate. Treatment or laboratory tests will be conducted at the discretion of the Investigator.

8.1.3.4 Notification to IRB of Serious Adverse Events

The investigator must comply with the applicable regulatory requirements related to the reporting of SAEs to the Institutional Review Board (IRB). The IRB must be informed in a timely manner by the investigator of SAEs occurring during the study. Investigators must also submit applicable safety information provided by [redacted] to their IRB. The final adjudication of an SAE will be conducted by [redacted] and the final Medwatch form will be sent to all sites for submission to their respective IRBs.

8.1.3.5 Reconciliation of Safety Data

All safety data will be reviewed throughout the study and information submitted on SAE report forms will be reconciled with data collected via the EDC system. Each SAE must have a corresponding AE recorded in the study database. Subject source documents will be reviewed during site audits and study monitoring visits to determine if there are any unreported AEs.

8.1.4 Laboratory Test Abnormalities

If an abnormal laboratory result indicated as clinically significant by the investigator is the reason for a subject being withdrawn from the study or requires treatment for the abnormality, this abnormal result must also be reported as an AE. In addition, any laboratory test result that meets the criteria for an SAE (see Section 8.1.1.3) must also be reported as an SAE so [redacted] can collect additional information about that abnormality, including information regarding relationship to test article or other causes, any action taken, and outcome.

8.1.5 Pregnancy

Women of childbearing potential include any female who has experienced menarche or is 18 years of age or older and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation [at least six months prior to initiation of treatment], or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea >12 consecutive months in women 50 years of age and older). Even women who are using one of the effective forms of birth control per protocol will be considered of childbearing potential.

Women of childbearing potential must have a urine pregnancy test prior to study enrollment and must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized. Prior to study enrollment, women of childbearing potential must be advised of the importance of avoiding pregnancy during the study and the potential risk factors for an unintentional pregnancy. The subject must sign an ICF documenting this discussion.

Women of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period). If a subject or investigator suspects that a subject may be pregnant at any time during the study, the test article must be withheld until the results of laboratory pregnancy testing are available. If pregnancy is confirmed, the subject must not receive or apply further test article and must be discontinued from the study.

If following initiation of study treatment, it is subsequently discovered that a study subject was pregnant or may have been pregnant at the time of test article exposure, the investigator must immediately notify the Medical Monitor of this event, and record the pregnancy on the appropriate pregnancy surveillance form. The form will be sent to [redacted]. The investigator must notify the IRB of any pregnancy associated with the study therapy and keep careful source documentation of the event.

Protocol-required procedures for those subjects that are discontinued from the study must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated, including

[redacted]

counseling of the subject by the investigator and her managing physician or health care provider (e.g., obstetrician). In addition, the investigator must report to [redacted], on the appropriate [redacted] pregnancy surveillance form(s), any follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Although pregnancy itself is not an AE, any complications during pregnancy should be recorded as AEs or SAEs (if they fulfill the SAE criteria). Offspring should be followed for a minimum of eight weeks. Any congenital anomaly/birth defect in a child born to a subject exposed to the test article(s) should be recorded as a SAE and details documented in the pregnancy surveillance form. Abortion, whether accidental, therapeutic, or spontaneous should be reported as a SAE.

8.2 Other Safety Concerns

The Contraindications, Warnings, Precautions, Drug Interactions, and Adverse Reactions associated with the use of metronidazole are described in the approved product labeling for metronidazole 0.75% vaginal gel (Oceanside Pharmaceutical). A brief summary of each is described Section 3.5.3.

9 STATISTICAL AND ANALYTICAL METHODS

The statistical analysis will be conducted by [redacted] in collaboration with Gage Development Company, LLC

A detailed statistical analysis plan will be finalized before the code for all subjects is broken and prior to locking the database to expand upon the statistical methods presented below. Any deviations from the analysis described below will be included in the SAP, which will be included in Appendix 16.1.9 of the clinical study report.

All baseline and efficacy data will be summarized and analyzed by treatment.

9.1 Sample Size

Assuming the test and reference clinical cure rates are within 4% of each other, the placebo clinical cure rate is 20%, the test and reference clinical cure rates are at least 36% and 12.4% of randomized subjects do not qualify for the modified Intent-to-Treat (mITT) population, then 603 subjects will be required to achieve at least 90% power for superiority and bioequivalence (Schwebke 2015; Chavoustie 2015). However, the previous studies that were used to estimate effect size had significant differences in study design and definition of primary endpoint. Taking these differences into consideration, 738 subjects will be randomized. The assumption of a 36% test and reference clinical cure rate was derived after review of the FDA statistical review of Metronidazole vaginal gel 1.3% (Center for Drug Evaluation and Research 2014).

9.2 Analysis Populations

The following subject populations will be created:

- Intent-to-Treat (ITT) Population: All randomized subjects.
- Safety Population: All subjects who receive at least 1 dose of study drug.
- Modified Intent-to-Treat (mITT) Population: All randomized subjects excluding those who subsequently demonstrate a positive test result for other concomitant vaginal or cervical infections at baseline (e.g. *C trachomatis*, *N. gonorrhoeae*) which may interfere with the efficacy assessment for BV or who have a baseline Nugent score < 4.
- Per Protocol (PP) Population: Includes all subjects who qualify for the mITT population and who follow important components of the trial (including subjects who adhere to treatment and follow-up for efficacy within the prescribed timeframe).

Subjects in the MITT population who discontinue early from the study and do not have an assessment of clinical cure and bacteriological cure will be included in the mITT population analyses as treatment failures. These subjects without outcomes, but are classified as treatment failures will not be included in the PP analyses.

To establish bioequivalence, the 90% confidence interval for the primary endpoint (the difference in the proportion of subjects achieving a clinical cure between metronidazole 0.75% vaginal gel (GDC-229; test product) and metronidazole 0.75% vaginal gel (Oceanside Pharmaceuticals) must be within [0.20, +0.20] for dichotomous variables, using the PP population.

9.3 Disposition of Subjects

The number of subjects who are enrolled and treated and complete the clinical trial will be tabulated. A disposition graph of subjects will be provided.

9.4 Demographic and Other Subject Characteristics

Subject demographics and pre-admission characteristics will be summarized descriptively.

9.5 Extent of Exposure

Exposure to study product will be summarized by the number of doses used and length of time over which the product is used.

9.6 Efficacy Analyses

9.6.1 Primary Endpoints

The primary endpoint is the clinical cure at the Test of Cure Visit (Visit 3) and includes the following:

- Resolution of the abnormal vaginal discharge to a normal physiologic discharge
- Negative whiff test
- Presence of clue cells at < 20% of the total epithelial cells on microscopic examination of the saline wet mount

The mITT population will be used to compare both the test and reference products to placebo. The PP population will be used to evaluate bioequivalence between the test and reference products.

To assess adequate study sensitivity the test and references products need to be statistically superior ($p<0.05$, 2-sided) to placebo using the mITT population.

To establish bioequivalence, the 90% confidence interval for the primary endpoint (the difference [test-reference] in clinical cure rate) must be within [-0.20, +0.20], using the PP population.

9.6.2 Secondary Endpoints

Secondary endpoints include the following as assessed at the Test of Cure (Visit 3):

- Nugent score of < 4
- Responder outcome (therapeutic cure) defined as follows:
  - Clinical cure as defined in the Primary Endpoint
  - Vaginal pH < 4.7
  - Nugent score of < 4 (i.e., bacteriological cure)

9.7 Safety Parameters

All safety analyses will be performed using the Safety Population.

9.7.1 Adverse Events

Safety will be evaluated by incidence of premature discontinuations and AEs. Summaries will be provided for all AEs reported, and separately for AEs leading to study discontinuation. Serious AEs will be listed separately and described by narrative.

9.7.2 Incidence of Adverse Events

The number (percentage) of subjects with at least one AE will be presented in a frequency table. Summaries will also be presented by relationship to the study treatment and intensity of AE.

9.7.3 Discontinuation Due to Adverse Events

Subjects who are discontinued due to an AE will be listed by research center. In cases where multiple AEs are involved in the discontinuation, the investigator must make a determination on which single AE was the primary reason for discontinuation. Specific information about the AEs will be included in the final clinical study report. A narrative for each AE leading to discontinuation will be provided.

9.7.4 Serious Adverse Events (SAEs)

Subjects with SAEs will be listed by center with the following variables included: SAE description (as reported by investigator), MedDRA "included" term, MedDRA "preferred" term, MedDRA system-organ class (based on the "include" term), start and stop days relative to the date of first dose, maximum intensity, relationship to the investigational, action taken with the study product per the investigator's judgment, and outcome.

9.7.5 Deaths

Subjects who die during the clinical trial will be listed by center with the following variables will be included: main reason(s) for death (as reported by the investigator), diagnosis of the SAE contributing to the death, date of death relative to the first day of product use, and relationship to investigational product. Subject SAE narratives will be part of the final clinical study report.

10 MEDICAL MONITOR

The Medical Monitor for this study is:

The Medical Monitor will be responsible for collaborating with the investigator and Sponsor to make determinations regarding subject eligibility, inclusion and exclusion criteria interpretations, and safety issues, and for managing reporting of the SAEs that occur in the study. A detailed medical monitoring plan will be written before the study begins.

11 ETHICAL AND REGULATORY CONSIDERATIONS

11.1 Compliance with Good Clinical Practice

All aspects of this multicenter clinical trial will be carried out in accordance with Good Clinical Practice (GCP) as required by the following: United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Parts 50, 54, 56, 312, and 320), ICH E6, and the 2013 revision of the Declaration of Helsinki.

These guidelines are on file at [redacted].

11.2 Interactions with Institutional Review Boards (IRBs)

This protocol will be reviewed by the IRB. This protocol and any protocol amendments, together with any required additional documentation (e.g., ICFs, subject information sheets, advertising materials, etc.), will be submitted by each site to its responsible IRB according to the applicable requirements at each site. The study will commence at each participating site only after its IRB has granted full approval. Investigators/institutions will permit trial-related monitoring, audits, IRB reviews, and regulatory inspection(s) and will provide direct access to source data and documents in order for these activities to be performed. No drug will be shipped to a site until written IRB authorization has been received by the Sponsor or its representative.

11.3 Informed Consent

Principal investigators must provide [redacted] (on behalf of Gage Development Company, LLC) with a copy of the ICF approved by their local IRB. All translations of Informed Consent documents should be certified.

Under informed consent, the subject shall understand that she is authorizing access to medical records as required for monitors, auditors, IRBs, and regulatory authorities. Subjects that agree to participate in the study must sign the ICF prior to study-specific procedures. The principles of informed consent will be implemented according to the 1996 revision of the Declaration of Helsinki, and FDA regulations. The sites must also follow Health Insurance Portability and Accountability Act (HIPAA) requirements in documenting subjects' authorization for the use of protected health information for study purposes.

It is the investigator's responsibility to assure that each subject is provided an explanation of the details contained in the informed consent statement and other locally-required documents prior to the individual signing the ICF certifying her voluntary participation in the trial and prior to study participation. Under informed consent, the subject shall understand that she is authorizing access to medical records as required for monitors, auditors, IRBs, and regulatory authorities.

The subjects will be informed of their right to privacy and the fact that personal information will be treated as strictly confidential and will not be publicly available in accordance with HIPAA regulations. They will also be informed that [redacted] and the FDA have the right to inspect and possibly photocopy their medical records to verify the accuracy and completeness of the clinical trial results. The subject is to receive a copy of the consent form after it has been signed and dated. The subject's copy can be unsigned if this is the requirement of the local IRB.

Prior to study participation, all study candidates will:

- Be informed of the nature and purpose of the study.
- Be given an explanation of the procedures to be followed in the study.
- Be given a description of any attendant discomforts and risks reasonably to be expected from the study, as well as from the study product.
- Be given an opportunity to ask any questions concerning the study.
- Be instructed that consent to participate in the study may be withdrawn by the participant at any time; and that the participant may discontinue participation in the study without prejudice.
- Be given a copy of the signed ICF.
- Be given the opportunity to decide to consent or not to consent to the study without coercion.
- Be given information for whom to contact if there are questions about the research, participant rights, or to report research-related injury.

11.4 Confidentiality

The information on individual subjects arising from this study is to be considered confidential and transmitted to the sponsor only in a form that will not permit identification of the individual. Regulatory and sponsoring agencies may request access to the study records and related medical records of each participating subject; the subject's identity will remain confidential to the extent permitted by the applicable laws and regulations. The results of the research will be released to public agencies including regulatory agencies, clinical investigators, and research organizations without reference to items identifiable to a particular subject. The results will be published such that the identity of the subjects will not be disclosed and cannot be ascertained. National and international agencies and sponsoring agencies may request access to the medical records of each participating subject, and if requested, the subject's identity will remain confidential. All records will be kept in a secure storage area with limited access.

[redacted]

12 STUDY MONITORING AND DOCUMENTATION

12.1 Clinical Monitoring, Quality Control, and Quality Assurance

Clinical monitoring will be completed by [redacted]. The principal investigator and sub-investigators will allow representatives from [redacted], local Clinical Research Organizations (CROs) contracted for the study access to all eCRFs, source documents, and corresponding portions of the medical records for each participant at mutually convenient times for periodic review during the study and after the study has been completed. The monitoring visits provide [redacted] or the local CROs with the opportunity to:

- Initiate the research center.
- Evaluate the progress of the study.
- Verify the accuracy and completeness of the eCRFs.
- Ensure that all protocol requirements, applicable FDA and other health authority regulations, and investigators' obligations are being fulfilled.
- Resolve any inconsistencies in the study records.
- Close out the trial at the research center.

In addition to routine monitoring, [redacted] or its designee on behalf of Gage Development Company, LLC may, at its discretion, perform site audits. The purpose of such audits will be to evaluate site trial conduct and compliance with the protocol, standard operating procedures (SOPs), GCP, and the applicable regulatory requirements. If an audit is performed, a site must provide the auditors with direct access to all relevant records and documentation related to the study.

12.2 Administrative and Record Management

All investigative site records will be kept in a secure and hazard-free storage area with limited access. Access will be restricted to personnel authorized to handle research documents. These records are to be retained for at least 2 years after approval of the marketing application or at least 2 years have elapsed since formal discontinuation of clinical development for this investigational product. [redacted] should be notified before destruction of any site records.

12.3 Study Documentation

Sites will maintain source documentation of all study visits and assessments completed for each subject. Source documentation data will be transcribed into the eCRFs.

[redacted] is responsible for assuring that the essential documents maintained in the trial master file at the research center are accurate and complete. Essential documents in the trial master files at [redacted] will be maintained according to written SOPs.

12.4 Electronic Data Capture (EDC) System/Data Transmission

EDC will be used to transmit data electronically from the site to the Data Coordinating Center at [redacted]. All requested information should be entered in the EDC system. Prior to the

start of the clinical trial, the investigator will complete an authorized signature sheet showing the signatures and handwritten initials of all individuals who are authorized to maintain study records and submit data using the EDC system. More detailed instructions regarding the EDC system will be provided by [redacted] in training and the instructions documents. The data in the database, including any updates as a result of data cleaning, will be compared to the source documents at subsequent monitoring visits.

12.5 Data Handling and Processing

Data handling will be completed by [redacted]. [redacted]' EDC system will be used to create, modify, maintain, archive, retrieve, and transmit study data generated for the clinical trial. The research centers will record clinical trial data (except for the central laboratory data) on an electronic web-based CRF (i.e., eCRF). Laboratory data from the central laboratory will be sent electronically to [redacted] and imported into a SAS® database maintained by the [redacted]' Biometrics Department. [redacted]' Data Management will follow written SOPs for processing EDC data. Archiving of the EDC data will be done by the EDC vendor.

12.6 Confidentiality and Reporting of Results

The information on individual subjects arising from this study is to be considered confidential and transmitted to the sponsor only in a form that will not permit identification of the individual. Regulatory and sponsoring agencies may request access to the study records and related medical records of each participating subject and the subject's identity will remain confidential to the extent permitted by the applicable laws and regulations. All records will be kept in a secure storage area with limited access.

The information obtained from the subjects that can be identified with the subject will remain confidential within the research team. Subject names will not be entered into the EDC system; instead, unique subject identifiers will be assigned to the subject. The results of the research will be released to public agencies including regulatory agencies, clinical investigators, and research organizations without reference to items identifiable to a particular subject. Medical records will be kept at the research center and will be available to study staff, [redacted], or the FDA only while at the study site. The results will be published such that the identity of the subjects will not be disclosed and cannot be ascertained. All data will only be used for the purpose for which it has been approved. Data collected during this study and any analyses of that data will not be used in any way other than those ways already approved without further approval from [redacted].

12.7 Retention of Data

The Investigator will maintain adequate records of the study including subjects' eCRFs, medical records, laboratory reports, consent form, drug disposition records, safety reports, information regarding participants who discontinued, and other pertinent data. All records are to be retained by the Investigator for a period of at least 2 years after the last approval of a marketing application or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product (per FDA CFR 312.62, "2 years after the investigation is discontinued and FDA is notified."). These documents should be retained for a

[redacted]

longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. The Investigator will contact [redacted] for authorization prior to destruction of any such records or in the event of accidental loss or destruction of any study records.

12.8 Publication Policy

Data on the use of the study medication and results of all clinical and laboratory studies are considered private and the confidential information of Sponsor. Any publications or presentations that result from this study will maintain participant confidentiality. Proprietary information about the investigational drug is maintained under the supervision of Sponsor. Institutions and/or the principal investigators agree to submit all proposed publications, papers, abstracts, manuscripts, posters or other written materials which include data relating to the Study or the use of the product supplied under this Agreement ("Proposed Publication"), including without limitation all outlines of any proposed oral presentations with respect thereto, to the Sponsor at least thirty (30) days prior to either (a) submission of such Proposed Publication (b) any proposed oral disclosure to a third party outside of [redacted]. The Sponsor shall have the right to comment on such Proposed Publications within (30) days of receipt, and such comments shall be considered in good faith by the principal investigators in determining the final form of disclosure. Upon request of Sponsor, Institution and/or principal investigator shall delay publication of such Proposed Publication an additional sixty (60) days to permit Sponsor to take necessary actions to protect its intellectual property interests. The Sponsor shall also have the right to eliminate any reference to confidential or proprietary information provided to Institutions and/or the principal investigators or the Study staff pursuant to this Agreement.

12.9 Reimbursement, Indemnity, and Insurance

Reimbursement, indemnity, and insurance are addressed in separate documentation.

12.10 Adherence to the Protocol

Except for a change that is intended to eliminate an immediate hazard to subjects, the approved protocol shall be conducted as described. All protocol deviations must be documented. Any protocol-related issues that pose an immediate or significant hazard to subjects must be reported to [redacted] on behalf of Gage Development Company, LLC immediately.

13 INVESTIGATOR OBLIGATIONS

Clinical research studies are subject to the regulations of the FDA. Prior to beginning the study, the investigator will be asked to demonstrate compliance with ICH E6, 8.2 and 21 CFR 312 by providing [redacted] with the signed essential documents required for the clinical trial. The responsibilities imposed upon investigators by the FDA are summarized in the "Statement of Investigator Form" (Form FDA-1572) which documents that he or she will follow the FDA regulations with respect to this study.

The investigator agrees to assume the responsibilities stated on the Form FDA-1572, and signifies his or her agreement by signing the Form FDA-1572, these responsibilities include:

- To conduct the study in accordance with the Study Protocol, Reference Drug Label, GCPs, International Conference on Harmonisation (ICH), and Declaration of Helsinki.
- To secure prior approval of the study by an appropriate IRB. This board should be constituted in conformity with FDA regulations.
- To report on the progress of the study to the IRB and to submit a final report within three months of the conclusion of data collection.
- To maintain current records of the receipt, dispensing, and disposition of study product and to return all unused product to the sponsor or the sponsor's designated agent.
- To obtain a valid, fully informed, freely given written consent from each subject who participates in the study.
- To maintain adequate study documentation, including hospital records, laboratory results and lab records, and to store these case histories for a minimum of two years following notification by the sponsor that all investigations have been discontinued or that the FDA has approved the drug application.
- To identify all sub-investigators who will also supervise drug administration.
- To report all AEs to the sponsor or designated agent promptly.
- To allow inspection or copying by the FDA, sponsor, or sponsor's designated agent of case histories and records of drug distribution.

Investigator Documentation required:

Prior to beginning the study, the investigator will be asked to comply with ICH E6, 8.2 and 21 CFR 312 by providing the following essential documents, including but not limited to:

1. A signed Protocol Signature Page.
2. A signed acknowledgement of receipt of the US Prescribing Information for the reference drug.
3. An IRB-approved Informed Consent.
4. IRB approval of protocol and ICF.
5. Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572.

6. Current Curriculum Vitae (CV) for the principal investigator and each sub-investigator listed on Form FDA 1572.
7. Medical license for principal investigator
8. A signed declaration of any financial conflict of interest (i.e., Financial Disclosure Form, financial disclosure).

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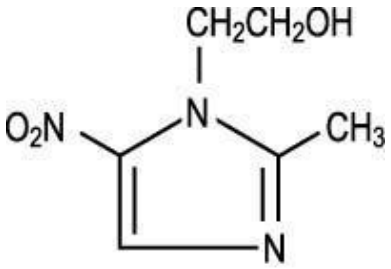
Appendix 1 U.S. PRESCRIBING INFORMATION FOR THE REFERENCE DRUG

METRONIDAZOLE- metronidazole gel
Oceanside Pharmaceuticals

Metronidazole Vaginal Gel, 0.75%
FOR INTRAVAGINAL USE ONLY
NOT FOR OPHTHALMIC, DERMAL, OR ORAL USE
DESCRIPTION
Metronidazole Vaginal Gel is the intravaginal dosage form of the synthetic antibacterial agent, metronidazole, USP at a concentration of 0.75%. Metronidazole is a member of the imidazole class of antibacterial agents and is classified therapeutically as an antiprotozoal and antibacterial agent. Chemically, metronidazole is a 2-methyl-5-nitroimidazole-1-ethanol. It has a chemical formula of $C_6H_9N_3O_3$, a molecular weight of 171.16, and has the following structure:



Metronidazole Vaginal Gel is a gelled, purified water solution, containing metronidazole at a concentration of 7.5 mg/g (0.75%). The gel is formulated at pH 4.0. The gel also contains carbomer 934P, edetate disodium, methylparaben, propylparaben, propylene glycol, and sodium hydroxide.

Each applicator full of 5 grams of vaginal gel contains approximately 37.5 mg of metronidazole.

CLINICAL PHARMACOLOGY

Normal Subjects:
Following a single, intravaginal 5 gram dose of metronidazole vaginal gel (equivalent to 37.5 mg of metronidazole) to 12 normal subjects, a mean maximum serum metronidazole concentration of 237 ng/mL was reported (range: 152 to 368 ng/mL). This is approximately 2% of the mean maximum serum metronidazole concentration reported in the same subjects administered a single, oral 500 mg dose of metronidazole (mean C = 12,785 ng/mL, range: 10,013 to 17,400 ng/mL). These peak concentrations were obtained in 6 to 12 hours after dosing with metronidazole vaginal gel and 1 to 3 hours after dosing with oral metronidazole.

The extent of exposure [area under the curve (AUC)] of metronidazole, when administered as a single intravaginal 5 gram dose of metronidazole vaginal gel (equivalent to 37.5 mg of metronidazole), was approximately 4% of the AUC of a single oral 500 mg dose of metronidazole (4977 ng-hr/mL and approximately 125,000 ng-hr/mL, respectively).

Dose-adjusted comparisons of AUCs demonstrated that, on a mg to mg comparison basis, the absorption of metronidazole, when administered vaginally, was approximately half that of an equivalent oral dosage.

Patients with Bacterial Vaginosis:
Following single and multiple 5 gram doses of metronidazole vaginal gel to 4 patients with bacterial vaginosis, a mean maximum serum metronidazole concentration of 214 ng/mL on day 1 and 294 ng/mL (range: 228 to 349 ng/mL) on day five were reported. Steady state metronidazole serum concentrations following oral dosages of 400 to 500 mg BID have been reported to range from 6,000 to 20,000 ng/mL.

Microbiology:
The intracellular targets of action of metronidazole on anaerobes are largely unknown. The 5-nitro group of metronidazole is reduced by metabolically active anaerobes, and studies have demonstrated that the reduced form of the drug interacts with bacterial DNA. However, it is not clear whether interaction with DNA alone is an important component in the bactericidal action of metronidazole on anaerobic organisms.

Culture and sensitivity testing of bacteria are not routinely performed to establish the diagnosis of bacterial vaginosis. (See **INDICATIONS AND USAGE**.)

Standard methodology for the susceptibility testing of the potential bacterial vaginosis pathogens, *Gardnerella vaginalis, Mobiluncus* spp., and *Mycoplasma hominis*, has not been defined. Nonetheless, metronidazole is an antimicrobial agent active in vitro against most strains of the following organisms that have been reported to be associated with bacterial vaginosis:

Bacteroides spp.

Gardnerella vaginalis

Mobiluncus spp.

Peptostreptococcus spp.

INDICATIONS AND USAGE
Metronidazole Vaginal Gel is indicated in the treatment of bacterial vaginosis (formerly referred to as Haemophilus vaginitis, Gardnerella vaginitis, nonspecific vaginitis, Corynebacterium vaginitis, or anaerobic vaginosis).

NOTE: For purposes of this indication, a clinical diagnosis of bacterial vaginosis is usually defined by the presence of a homogeneous vaginal discharge that (a) has a pH of greater than 4.5, (b) emits a “fishy” amine odor when mixed with a 10% KOH solution, and (c) contains clue cells on microscopic examination. Gram’s stain results consistent with a diagnosis of bacterial vaginosis include (a) markedly reduced or absent Lactobacillus morphology, (b) predominance of Gardnerella morphotype, and (c) absent or few white blood cells.

Other pathogens commonly associated with vulvovaginitis, e.g., *Trichomonas vaginalis, Chlamydia trachomatis, N. gonorrhoeae, Candida albicans,* and *Herpes simplex* virus should be ruled out.

CONTRAINDICATIONS
Metronidazole Vaginal Gel is contraindicated in patients with a prior history of hypersensitivity to metronidazole, parabens, other ingredients of the formulation, or other nitroimidazole derivatives.

WARNINGS
Convulsive Seizures and Peripheral Neuropathy:
Convulsive seizures and peripheral neuropathy, the latter characterized mainly by numbness or paresthesia of an extremity, have been reported in patients treated with oral or intravenous metronidazole. The appearance of abnormal neurologic signs demands the prompt discontinuation of metronidazole vaginal gel therapy. Metronidazole vaginal gel should be administered with caution to patients with nervous system diseases.

Psychotic Reactions:
Psychotic reactions have been reported in alcoholic patients who were using oral metronidazole and disulfiram concurrently. Metronidazole vaginal gel should not be administered to patients who have taken disulfiram within the last two weeks.

PRECAUTIONS
Metronidazole Vaginal Gel affords minimal peak serum levels and systemic exposure (AUCs) of metronidazole compared to 500 mg oral metronidazole dosing. Although these lower levels of exposure are less likely to produce the common reactions seen with oral metronidazole, the possibility of these and other reactions cannot be excluded presently. Data from well-controlled trials directly comparing metronidazole administered orally to metronidazole administered vaginally are not available.

General:
Patients with severe hepatic disease metabolize metronidazole slowly. This results in the accumulation of metronidazole and its metabolites in the plasma. Accordingly, for such patients, metronidazole vaginal gel should be administered cautiously.

Known or previously unrecognized vaginal candidiasis may present more prominent symptoms during therapy with metronidazole vaginal gel. Approximately 6-10% of patients treated with Metronidazole Vaginal Gel developed symptomatic Candida vaginitis during or immediately after therapy.

Disulfiram-like reaction to alcohol has been reported with oral metronidazole, thus the possibility of such a reaction occurring while on metronidazole vaginal gel therapy cannot be excluded.

Metronidazole Vaginal Gel contains ingredients that may cause burning and irritation of the eye. In the event of accidental contact with the eye, rinse the eye with copious amounts of cool tap water.

Information for the Patient:
The patient should be cautioned about drinking alcohol while being treated with metronidazole vaginal gel. While blood levels are significantly lower with Metronidazole Vaginal Gel than with usual doses of oral metronidazole, a possible interaction with alcohol cannot be excluded.

The patient should be instructed not to engage in vaginal intercourse during treatment with this product.

Drug Interactions:
Oral metronidazole has been reported to potentiate the anticoagulant effect of warfarin and other coumarin anticoagulants, resulting in a prolongation of prothrombin time. This possible drug interaction should be considered when metronidazole vaginal gel is prescribed for patients on this type of anticoagulant therapy.

In patients stabilized on relatively high doses of lithium, short-term oral metronidazole therapy has been associated with elevation of serum lithium levels and, in a few cases, signs of lithium toxicity.

Use of cimetidine with oral metronidazole may prolong the half-life and decrease plasma clearance of metronidazole.

Drug/Laboratory Test Interactions:
Metronidazole may interfere with certain types of determinations of serum chemistry values, such as aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), lactate dehydrogenase (LDH), triglycerides, and glucose hexokinase. Values of zero may be observed. All of the assays in which interference has been reported involve enzymatic coupling of the assay to oxidation-reduction of nicotinamide-adenine dinucleotides (NAD + NADH). Interference is due to the similarity in absorbance peaks of NADH (340 nm) and metronidazole (322 nm) at pH 7.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Metronidazole has shown evidence of carcinogenic activity in a number of studies involving chronic oral administration in mice and rats. Prominent among the effects in the mouse was the promotion of pulmonary tumorigenesis. This has been observed in all six reported studies in that species, including one study in which the animals were dosed on an intermittent schedule (administration during every fourth week only). At very high dose levels (approximately 500 mg/kg/day), there was a statistically significant increase in the incidence of malignant liver tumors in males. Also, the published results of one of the mouse studies indicate an increase in the incidence of malignant lymphomas as well as pulmonary neoplasms associated with lifetime feeding of the drug. All these effects are statistically significant. Several long-term oral dosing studies in the rat have been completed. There were statistically significant increases in the

incidence of various neoplasms, particularly in mammary and hepatic tumors, among female rats administered metronidazole over those noted in the concurrent female control groups. Two lifetime tumorigenicity studies in hamsters have been performed and reported to be negative. These studies have not been conducted with 0.75% metronidazole vaginal gel, which would result in significantly lower systemic blood levels than those obtained with oral formulations.

Although metronidazole has shown mutagenic activity in a number of in vitro assay systems, studies in mammals (in vivo) have failed to demonstrate a potential for genetic damage.

Fertility studies have been performed in mice up to six times the recommended human oral dose (based on mg/m2) and have revealed no evidence of impaired fertility.

Pregnancy: Teratogenic Effects:

Pregnancy Category B

There has been no experience to date with the use of Metronidazole Vaginal Gel in pregnant patients. Metronidazole crosses the placental barrier and enters the fetal circulation rapidly. No fetotoxicity or teratogenicity was observed when metronidazole was administered orally to pregnant mice at six times the recommended human dose (based on mg/m2); however, in a single small study where the drug was administered intraperitoneally, some intrauterine deaths were observed. The relationship of these findings to the drug is unknown.

There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, and because metronidazole is a carcinogen in rodents, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers:
Specific studies of metronidazole levels in human milk following intravaginally administered metronidazole have not been performed. However, metronidazole is secreted in human milk in concentrations similar to those found in plasma following oral administration of metronidazole.

Because of the potential for tumorigenicity shown for metronidazole in mouse and rat studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:
Safety and effectiveness in children have not been established.

ADVERSE EVENTS

Clinical Trials:

There were no deaths or serious adverse events related to drug therapy in clinical trials involving 800 non-pregnant women who received Metronidazole Vaginal Gel.

In a randomized, single-blind clinical trial of 505 non-pregnant women who received Metronidazole Vaginal Gel once or twice a day, 2 patients (one from each regimen) discontinued therapy early due to drug-related adverse events. One patient discontinued drug because of moderate abdominal cramping and loose stools, while the other patient discontinued drug because of mild vaginal burning. These symptoms resolved after discontinuation of drug.

Medical events judged to be related, probably related, or possibly related to administration of Metronidazole Vaginal Gel once or twice a day were reported for 195/505 (39%) patients. The incidence of individual adverse reactions were not significantly different between the two regimens. Unless percentages are otherwise stipulated, the incidence of individual adverse reactions listed below was less than 1%:

Reproductive:

Vaginal discharge (12%),

Symptomatic *Candida* cervicitis/vaginitis (10%),

Vulva/vaginal irritative symptoms (9%),

Pelvic discomfort (3%).

Gastrointestinal:

Gastrointestinal discomfort (7%),

Nausea and/or vomiting (4%),

Unusual taste (2%),

Diarrhea/loose stools (1%),

Decreased appetite (1%),

Abdominal bloating/gas; thirsty, dry mouth.

Neurologic:

Headache (5%), Dizziness (2%), Depression.

Dermatologic:

Generalized itching or rash.

[redacted]

Other:

Unspecified cramping (1%),

Fatigue,

Darkened urine.

In previous clinical trials submitted for approved labeling of Metronidazole Vaginal Gel the following was also reported:

Laboratory:

Increased/decreased white blood cell counts (1.7%).

Other Metronidazole Formulations:

Other effects that have been reported in association with the use of topical (dermal) formulations of metronidazole include skin irritation, transient skin erythema, and mild skin dryness and burning. None of these adverse events exceeded an incidence of 2% of patients.

Metronidazole Vaginal Gel affords minimal peak serum levels and systemic exposure (AUC) of metronidazole compared to 500 mg oral metronidazole dosing. Although these lower levels of exposure are less likely to produce the common reactions seen with oral metronidazole, the possibility of these and other reactions cannot be excluded presently.

The following adverse reactions and altered laboratory tests have been reported with the **oral or parenteral** use of metronidazole:

Cardiovascular: Flattening of the T-wave may be seen in electrocardiographic tracings.

Central Nervous System: (See **WARNINGS**.) Headache, dizziness, syncope, ataxia, confusion, convulsive seizures, peripheral neuropathy, vertigo, incoordination, irritability, depression, weakness, insomnia.

Gastrointestinal: Abdominal discomfort, nausea, vomiting, diarrhea, an unpleasant metallic taste, anorexia, epigastric distress, abdominal cramping, constipation, “furry” tongue, glossitis, stomatitis, pancreatitis, and modification of taste of alcoholic beverages.

Genitourinary: Overgrowth of Candida in the vagina, dyspareunia, decreased libido, proctitis.

Hematopoietic: Reversible neutropenia, reversible thrombocytopenia.

Hypersensitivity Reactions: Urticaria; erythematous rash; flushing; nasal congestion; dryness of the mouth, vagina, or vulva; fever; pruritus; fleeting joint pains.

Renal: Dysuria, cystitis, polyuria, incontinence, a sense of pelvic pressure, darkened urine.

[redacted]

OVERDOSAGE
There is no human experience with overdosage of metronidazole vaginal gel. Vaginally applied metronidazole gel, 0.75% could be absorbed in sufficient amounts to produce systemic effects. (See **WARNINGS.**)

DOSAGE AND ADMINISTRATION
The recommended dose is one applicator full of Metronidazole Vaginal Gel (approximately 5 grams containing approximately 37.5 mg of metronidazole) intravaginally once or twice a day for 5 days. For once-a-day dosing, Metronidazole Vaginal Gel should be administered at bedtime.

HOW SUPPLIED
Metronidazole Vaginal Gel 0.75% is supplied in a 70 gram tube and packaged with 5 vaginal applicators.

The NDC number for the 70 gram tube is 68682-455-70.

Store at controlled room temperature 15° to 30°C (59° to 86°F). Protect from freezing.

Clinical Studies

In a randomized, single-blind clinical trial of non-pregnant women with bacterial vaginosis who received Metronidazole Vaginal Gel daily for 5 days, the clinical cure rates for evaluable patients determined at 4 weeks after completion of therapy for the QD and BID regimens were 98/185 (53%) and 109/190 (57%), respectively.

Rx Only
Manufactured for: Valeant Pharmaceuticals North America LLC, Bridgewater, NJ 08807
By: DPT Laboratories, Inc., San Antonio, TX 78215
Rev. 11/14

DIRECTIONS FOR USE

1. Filling the applicator

- Remove cap and puncture metal seal on tube with the pointed tip of cap. (See Figure 1)
- Screw end of applicator onto tube. (See Figure 2)
- Slowly squeeze gel out of tube and into applicator. Plunger will stop when the applicator is full. (See Figure 3)
- Unscrew applicator and replace cap on tube.

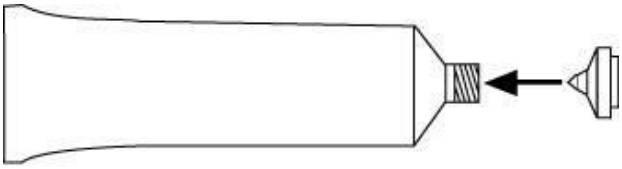


Figure 1

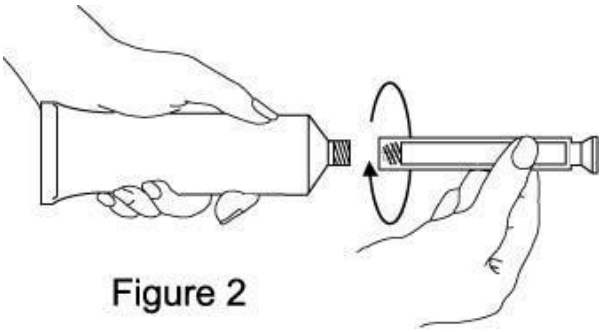


Figure 2

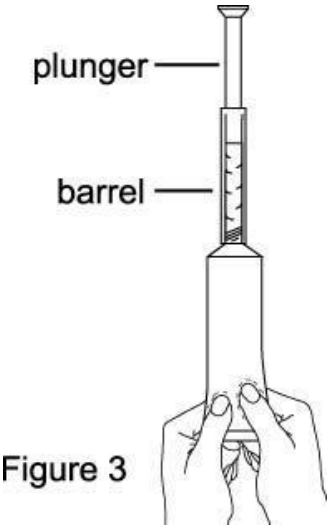


Figure 3

2. Inserting the applicator

- The applicator may be inserted while lying on your back with your knees bent or in any comfortable position
- Hold filled applicator by barrel, and gently insert into vagina as far as it will comfortably go. (See Figure 4)
- Slowly press the plunger until it stops to deposit gel into vagina and then withdraw the applicator.

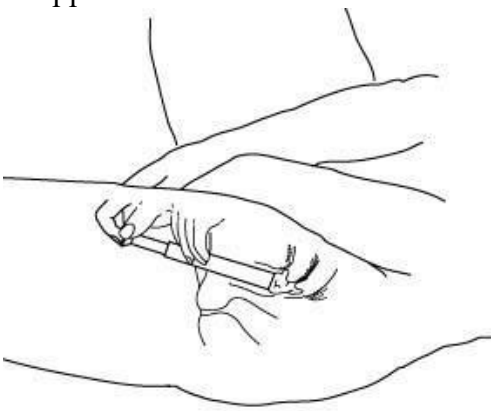


Figure 4

3. Care of the applicator

If physician prescribes twice-a-day dosing:

- After use, pull the plunger out of the barrel. (See Figure 5)
- Wash both plunger and barrel in warm soapy water and rinse thoroughly.
- To reassemble applicator, gently push plunger back into barrel.

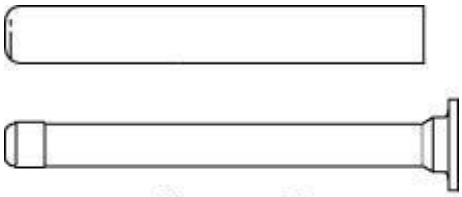


Figure 5

IMPORTANT:

For once-a-day dosing, apply one applicator full at bedtime. For twice-a-day dosing, apply one applicator full each morning and evening for five days, or as directed by physician.

[redacted]

WARNINGS:

- If significant irritation develops from the use of this medication, discontinue use and consult your physician.
- Do not use during pregnancy except under the supervision of a physician.
- Keep this and all medications out of reach of children.
- For vaginal use only. Not for use in the eyes, on the skin or in the mouth.

Store at room temperature. Avoid exposure to extreme heat or cold.

See end of carton and bottom of tube for lot number and expiration date.

Manufactured for: Valeant Pharmaceuticals North America LLC, Bridgewater, NJ 08807

By: DPT Laboratories, Inc., San Antonio, TX 78215

Rev. 11/14
9432501
140410-1114

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL - 70 gram Carton

NDC 68682-455-70

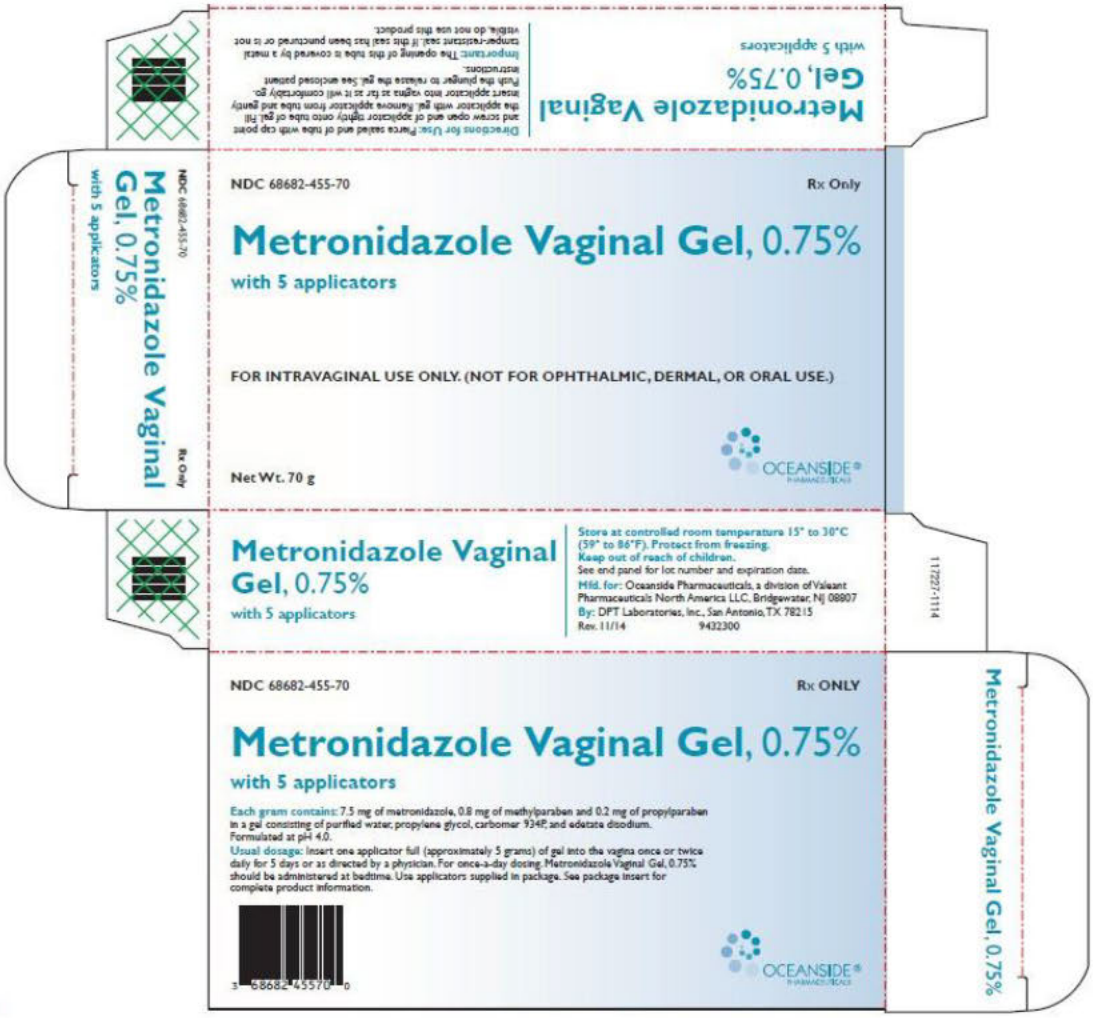
Rx Only

Metronidazole Vaginal Gel, 0.75%
with 5 applicators

FOR INTRAVAGINAL USE ONLY. (NOT FOR OPHTHALMIC, DERMAL, OR ORAL USE.)

Net Wt. 70 g

OCEANSIDE PHARMACEUTICALS®



METRONIDAZOLE metronidazole gel			
Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:68682-455
Route of Administration	VAGINAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
METRONIDAZOLE (UNII: 140 QMO216 E) (METRONIDAZOLE - UNII:140 QMO216 E)	METRONIDAZOLE	7.5 mg in 1 g

[redacted]

Inactive Ingredients

Ingredient Name	Strength
CARBOMER 9 3 4 (UNII: Z135WT9 20 8)	
EDETATE DISODIUM (UNII: 7FLD9 1C8 6 K)	
METHYLPARABEN (UNII: A2I8 C7HI9 T)	
PROPYLPARABEN (UNII: Z8 IX2SC1OH)	
PROPYLENE GLYCOL (UNII: 6 DC9 Q 16 7V3)	
SODIUM HYDRO XIDE (UNII: 55X0 4QC32I)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68682-455-70	70 g in 1 TUBE, WITH APPLICATOR		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA AUTHORIZED GENERIC	NDA020208	04/01/2015	

Labeler - Oceanside Pharmaceuticals (832011691)

Establishment

Name	Address	ID/FEI	Business Operations
DPT Laboratories, Ltd.		832224526	MANUFACTURE (68682-455)

Revised: 4/2015 Oceanside Pharmaceuticals

[redacted]

Appendix 2 SUBJECT DOSING INSTRUCTIONS FOR STUDY MEDICATION

SUBJECT DOSING INSTRUCTIONS FOR STUDY MEDICATION
Bacterial Vaginosis Study
Protocol GDC-229-002

Please follow these instructions exactly as they are written below. Contact the study staff at the telephone number below if you have any questions about the study.

Name: _____Phone: _____

Your study medication kit includes a 70 gram tube of study medicine and 5 vaginal applicators. The study medicine is to be applied into the vagina using a new applicator each night at bedtime for five consecutive nights. You will start on the same day that you were given this medication by the study site.

NOTE: It is important for you to continue to use the study medication during the prescribed 5-day treatment period unless directed to do otherwise by the study doctor. Do not discontinue the use of the medication unless directed so by the study staff. Talk to the study staff about any side effects that you experience.

- You should not drink alcohol on Days 1 to 6 (during the five days of treatment and for one day afterward).
- You should not engage in sexual intercourse
  - on Days 1 to 7 (during five days of treatment and for two days afterward) or
  - 48 hours before Visit 2 and Visit 3.
- **Do not use any intravaginal product** other than study medication **for the duration of this trial**. This includes: spermicide, tampon, douche, feminine deodorant spray, diaphragm, vaginal ring birth control, or condom with spermicide.
- Do not insert into the vagina any drug (e.g. Monistat, etc.), or non-drug product during this study; also do not use any topical vaginal products (e.g., hydrocortisone, etc.) for the duration of this trial.
- If you miss a dose, take the next dose at the usual time the following evening. Report any missed doses to the study staff at your next visit.
- It is recommended to empty bladder completely prior to administering study drug.
- If significant irritation develops from the use of this medication consult the study doctor.
- Keep this and all medications out of reach of children.
- Do not allow anyone else to use this study medication.
- For vaginal use only. Not for use in the eyes, on the skin or in the mouth.
- Store the study medication at room temperature.

Study Visit Schedule:

Visit	Calendar Day	Date	Time
2			
3			

Bring this instruction sheet, unused study medication, and any unused applicators to each study visit.

Step 1 <u>Fill the applicator</u>

a) You have been given five (5) applicators -- one for each night that you will need to use the study medication.
b) Remove the cap from the tube of study medication and puncture the metal seal on the top of the tube with the pointed tip of the cap. (See Figure 1)
c) Screw the end of one applicator completely onto the tube. (See Figure 2)
d) Slowly squeeze the gel out of the tube and into the applicator until the plunger stops moving (the plunger will stop when the applicator is full). (See Figure 3)
e) Unscrew the applicator and replace the cap onto the tube.

Figure 1

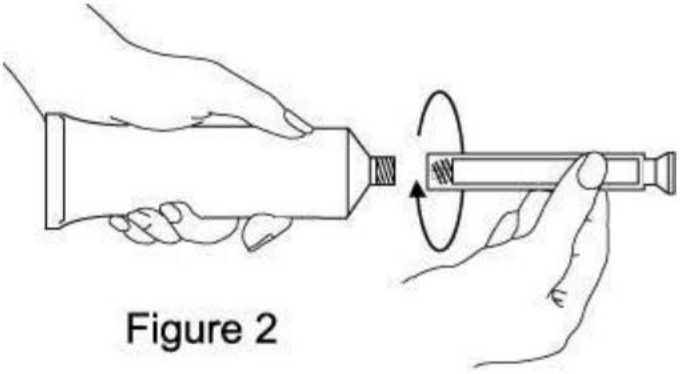


Figure 2

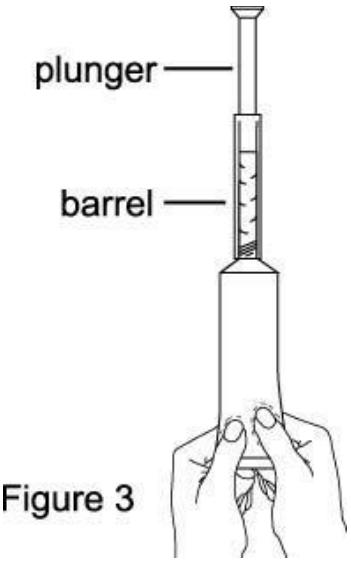


Figure 3

Step 2 <u>Insert the applicator</u>

a) The applicator may be inserted while lying on your back with your knees bent or in any comfortable position.
b) Hold the filled applicator by the applicator barrel and gently insert it into your vagina as far as it will comfortably go. (See Figure 4)
c) Slowly press the plunger until it stops in order to insert all of the gel into your vagina and then withdraw the applicator.
d) Throw away the used applicator. Do not reuse it.

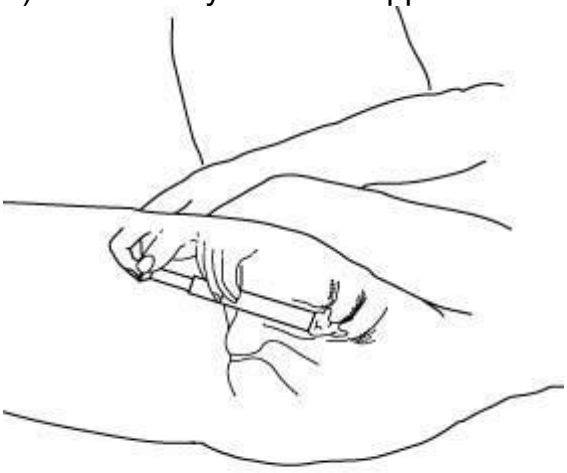


Figure 4

Step 3 <u>Return Instructions</u>

a) Return the tube of remaining study medication with all original packaging to the study site at your next visit.
b) Return all **unused** applicators to the study site at your next visit.