CLINICAL STUDY PROTOCOL

Protocol No. SYM-1219-401

A Multi-Center, Open-Label Study to Evaluate the Safety of a Single Oral Dose of Solosec™ (secnidazole) 2g Oral Granules for the Treatment of Adolescent Girls with Bacterial Vaginosis

Protocol Version (Date): Version 1.0, 23 March 2018

Amendment(s) (Date(s)): NA

Sponsor: Lupin Research Inc.
111 S Calvert St Ste 2100
Baltimore, MD 21202

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and clinical research guidelines established by the Code of Federal Regulations (Title 21, CFR Parts 50, 56 and 312) and ICH Guidelines. All investigators will agree to comply with US Federal Regulations concerning written informed consent and the rights of human subjects as outlined in CFR Part 50. Essential study documents will be archived in accordance with applicable country regulations.

SPONSOR SIGNATORY

Signed: _____ Date: 26 March 2018

Gregory Kaufman, MD
Senior Vice President
Global Medical Affairs - Specialty
Lupin Research Inc.

INVESTIGATOR AGREEMENT

A Multi-Center, Open-Label Study to Evaluate the Safety of a Single Oral Dose of Solosec (secnidazole) 2g Oral Granules for the Treatment of Adolescent Girls with Bacterial Vaginosis

Protocol Number: SYM-1219-401

IND Number: 117811

I have carefully read the foregoing protocol including all appendices and agree that it contains all the necessary information for conducting the study safely.

I will conduct this study in strict accordance with this protocol and according to the current GCP guidelines and will attempt to complete the study within the time designated.

I will provide copies of the protocol and all other information submitted by the Sponsor relating to pre-clinical and prior clinical experience to all personnel for whom I am responsible that participate in the study. I will discuss this information with them to assure that they are adequately informed regarding the drug and conduct of the study.

I agree to keep records on all subject information (case report forms, shipment and drug return forms and all other information collected during the study) in accordance with the current GCP and local regulations.

Principal Investigator's name	Lupin Representative's name
Signature	Signature
Date (dd-Mmm-yyyy)	Date (dd-Mmm-yyyy)
Institution	

TABLE OF CONTENTS

1. SYNOPSIS

Protocol Number	SYM-1219-401
Title of Study	A Multi-Center, Open-Label Study to Evaluate the Safety of a Single Oral Dose of Solosec™ (secnidazole) 2g Oral Granules for the Treatment of Adolescent Girls with Bacterial Vaginosis
Name of Active Ingredient(s)	Secnidazole
IND/EudraCT No.	117811
Indication	Bacterial vaginosis
Phase of Development	Phase 4
Investigational Center(s)	Approximately 5-10 study centers in the United States
Objectives Primary Objective	The objective of this study is to evaluate safety of single oral dose of Solosec™ (secnidazole) 2g oral granules for the treatment of adolescent girls with bacterial vaginosis.
Secondary Objective	Secondary assessments of efficacy will be assessed.
Study Design Overview	This is a multi-center, open-label study to evaluate the safety of Solosec in adolescent girls with bacterial vaginosis. Approximately 40 patients will be enrolled. Patients determined to be eligible at the Baseline Visit (Day 1) will receive a single oral dose of Solosec™ granules (containing 2 grams of secnidazole) on Day 1. Patients will return to the site once between Days 7-14 for a "test of cure" (TOC) Visit. A follow-up telephone call will be performed at Days 21-30 to assess the continued clinical response to treatment and adverse events (See Schedule of Assessments table for a complete list and timing of assessments and tests).
Number of Patients Planned	Approximately 40 patients will be enrolled.
Diagnosis and Main Criteria for Enrollment Inclusion Criteria	1. Are adolescent girls 12-17 years of age. 2. Are willing and able to give written informed assent with a written informed consent from a parent or legal guardian. 3. Are in good general health including as confirmed by a medical history and physical examination, with no known medical or mental health conditions that, in the Investigator's opinion, may interfere with study participation. 4. Willing and able to participate in the study as an outpatient, make required visits to the study center, and comply with all study requirements. 5. Have a negative urine pregnancy test result prior to study treatment initiation. In addition, female patients of childbearing potential must be using an acceptable form of birth control as determined by the Investigator (e.g., oral contraception, implantable, injectable or transdermal hormonal contraception, intrauterine device [IUD], double-barrier methods, have a vasectomized partner or abstinence [if the patient becomes sexually active they must use one of the acceptable methods of birth control]). Note: NuvaRing® or any other vaginal ring products are not permitted. 6. Have a clinical diagnosis of bacterial vaginosis, defined as having

	all of the following criteria: a. Off-white (milky or gray), thin, homogeneous vaginal discharge AND b. Vaginal pH > 4.5 AND c. Presence of Clue cells of ≥ 20% of the total epithelial cells on microscopic examination of the vaginal saline wet mount AND d. A positive 10% KOH Whiff test. 7. Agree to abstain from vaginal intercourse until after the TOC visit. 8. Agree not to have any vaginal penetration or use of any vaginal products until after the TOC visit (e.g., spermicides, condoms, diaphragms, vibrators, tampons, etc.). 9. Agree not to use vaginal douches or similar products for the duration of the study.
Exclusion Criteria	A subject who meets any of the following exclusion criteria must not be enrolled: 1. Are pregnant, lactating, or planning to become pregnant during the study. 2. Are menstruating or have vaginal bleeding at the Baseline Visit (Day 1). 3. Are menopausal as determined by the Investigator 4. Are suspected clinically (or confirmed diagnostically) of having alternative causes of vaginal symptoms including candidiasis, Chlamydia trachomatis, Trichomonas vaginalis, Neisseria gonorrhoeae or Herpes simplex or human papilloma virus. 5. Have active genital lesions, including active Herpes simplex lesions, or other vaginal or vulvar conditions which could confound the interpretation of the clinical response, as determined by the Investigator (patients with genital warts that are not being treated may be enrolled). 6. Have received antifungal or antimicrobial therapy (systemic or intravaginal) within 14 days prior to the Baseline Visit (Day 1). 7. Are using NuvaRing® or any other vaginal ring products. 8. Have consumed any alcohol within 12 hours prior to treatment with study medication. 9. Have a history of drug or alcohol abuse within the past 6 months, as determined by the Investigator. 10. Have participated in any investigational trial within 30 days or six half-lives of the test drug's biologic activity, whichever is longer, before the Baseline Visit (Day 1). 11. Are participating in any investigational, observational or non-interventional study (either currently or during the study). 12. Have had previous exposure to SYM-1219 or participation in other clinical trials of SYM-1219. 13. Have a known allergy to nitroimidazoles (e.g., metronidazole, tinidazole, nimorazole, etc.). 14. Have a history of an abnormal Pap smear which required cervical biopsy or cervical cauterization within 3 months of the Baseline Visit (Day 1). 15. Have any history of cervical carcinoma or other carcinomas of the

	vagina or vulva. 16. Have any condition that interferes with their ability to understand or comply with the requirements of the study.
Study Endpoints Efficacy Endpoints	Although this study is primarily an observational safety study, some efficacy endpoints will be evaluated at the TOC Visit (Study Day 7-14) including: • Clinical Outcome: A Clinical Outcome Responder is defined as a patient with all of the following: 1) Resolution of abnormal vaginal discharge, and 2) Negative 10% KOH Whiff test; and 3) Clue cells less than 20% of the total epithelial cells on microscopic examination of the vaginal wet mount using saline. • Nugent Score - TOC Visit [Study Day 7-14] score of 0-3 will be considered normal; a score of 4 and above will be considered abnormal. • Investigator's Clinical Assessment - TOC Visit [Study Day 7-14]: Investigator's opinion of the need for additional BV treatment (Yes or No). • Patient's Continued Clinical Response - Study Day 21-30 only: Investigator's opinion of the continued clinical response to treatment (Yes or No)
Safety Endpoints	• Adverse events (AEs): Includes treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), treatment-related AEs, and AEs leading to study discontinuation. • Vital signs: Blood pressure, temperature and pulse. • Physical Examinations • Pelvic Examinations: External genitalia and vagina • Laboratory assessments: Includes serum chemistry, hematology and urinalysis
Investigational Product, Dose, and Mode of Administration	Solosec™ 2 grams, oral
Reference Product, Dose, and Mode of Administration	NA
Placebo Product, Dose, and Mode of Administration	NA
Statistical Methods Sample Size Determination	The sample size was chosen to provide observational safety data only. No formal sample size calculations were made
Analysis of Primary Endpoint	Safety analyses will include assessment of adverse events, vital signs, pelvic examination, and laboratory assessments. The Safety population will be composed of all enrolled patients who received the study medication.

Table 1 Schedule of Assessments

Assessment	Baseline Visit	Test of Cure (TOC) / EOS Assessment	Patient Telephone Interview
	Day 1	Day 7-14	Day 21-30
Informed consent/assent	X		
Inclusion/exclusion	X		
Demographics	X		
Medical history	X		
Vital signs	X	X	
Height/weight	X		
Urine pregnancy test[1]	X	X	
Physical examination	X	X[5]	
Pelvic examination	X	X	
External genitalia and vaginal exam	X	X	
Vaginal discharge assessment	X	X	
Vaginal wet mount for Clue cell assessment	X	X	
Gram stain of vaginal fluid	X[2]	X	
10% KOH Whiff test	X	X	
pH of vaginal fluid	X		
STI Assessments	X	X[3]	
OSOM® Trichomonas Rapid Test	X[4]		
Bimanual pelvic examination	X	X[6]	
Labs: Hematology, chemistry, and urinalysis	X[2]	X	
Drug dosing	X		
Concomitant medication review	X	X	X
Adverse events query	X	X	X
Telephone interview of patient			X
Investigator's Clinical Assessment		X	

1. Performed by site personnel (not sent to central laboratory).
2. Results will not be available at the time of enrollment.
3. Only as indicated as determined by the Investigator.
4. It is recommended that the vaginal sample for the OSOM® Trichomonas Rapid Test be obtained early in the collection process to ensure adequate sample for this evaluation.
5. A targeted physical examination at the TOC/EOS Visit is only needed per the Investigator's discretion if a reported AE requires further evaluation.
6. A bimanual pelvic examination is required for all patients at Baseline and will be performed after the vaginal discharge assessment and all vaginal samples have been collected. At the Investigator's discretion, a bimanual pelvic examination may be performed at the TOC/EOS Assessment after the vaginal discharge assessment and all of the vaginal samples have been collected.

2. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine transaminase
API	Active pharmaceutical ingredient
AST	Aspartate transaminase
bpm	Beats per minute
BV	Bacterial vaginosis
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CMH	Cochran-Mantel-Haenszel
CRA	Clinical Research Associate
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
EOS	End of Study visit
EU	European Union
FDA	Food and Drug Administration
g	Gram
GCP	Good Clinical Practice
HEENT	Head, eyes, ears, nose, and throat
HIPAA	Health Insurance Portability and Accountability Act
HPV	Human papillomavirus
HSV-1	Herpes simplex virus type 1
HSV-2	Herpes simples virus type 2
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine Device
kg	Kilograms
KOH	Potassium hydroxide
LCM	Local Clinical Management
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mITT	Modified Intent-to-Treat
OTC	Over-the-counter
PID	Pelvic inflammatory disease
PO	Oral
PP	Per-Protocol
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	System Organ Class
STI(s)	Sexually transmitted infection(s)
TEAE	Treatment-emergent adverse event
TOC	Test of Cure
US	United States
USP	United States Pharmacopeia
WBC	White blood cell count

3. INTRODUCTION

3.1 BACKGROUND

Solosec (secnidazole, SYM-1219) 2g oral granules is a FDA approved treatment for bacterial vaginosis (BV) in adult women. Solosec™ is a potent, 5-nitroimidazole antibiotic with enhanced pharmacokinetic properties that enable delivery in a single dose that has been shown to be efficacious and well tolerated.

BV is the most prevalent gynecologic infection in the U.S., affecting 21 million women ages 14 to 49 annually (Koumans, 2007). If left untreated, BV can increase the risk of contracting sexually transmitted diseases, including chlamydia, gonorrhea, herpes, trichomaniasis and HIV, and can also increase the risk of pre-term birth and low birth weight (CDC). More than 50 percent of women treated for BV have a recurrence within 12 months, significantly impacting work productivity and quality of life (IMS, 2014). In recent studies, 60 percent of recurrent sufferers reported a negative impact on work attendance, job performance and productivity, and 95 percent reported a severe restriction in intimate partner relations (Payne, 2010).

The FDA approval was supported by a comprehensive set of studies, including two pivotal trials in BV and an open label safety study, which found efficacy for single-dose secnidazole 2g. All treatment emergent adverse events were mild or moderate in intensity; no serious adverse events were reported, and no patients discontinued treatment due to adverse events (Hillier, 2017; Schwebke, 2017).

3.2 CLINICAL EXPERIENCE WITH SYM-1219

Two randomized placebo-controlled clinical trials (Trial 1 and Trial 2) with similar designs were conducted to evaluate the efficacy of Solosec 2g for the treatment of bacterial vaginosis (Solosec Package Insert, Appendix A]. A diagnosis of bacterial vaginosis was defined as all of (a) the presence of an off-white (milky or gray), thin, homogeneous vaginal discharge; (b) a vaginal pH $\geq$ 4.7; (c) the presence of Clue cells $\geq$ 20% of the total epithelial cells on a microscopic examination of the vaginal saline wet mount; (d) a positive "whiff" test (detection of amine odor on addition of 10% KOH solution to a sample of the vaginal discharge); and (e) a Nugent score > 4. Trial 1 enrolled 144 non-pregnant female patients aged 19 to 54 years and Trial 2 enrolled 189 non-pregnant females aged 18 to 54 years. Black or African American subjects in both trials were 54%. Efficacy was assessed by clinical outcome evaluated 21 to 30 days following a single dose of Solosec. A Clinical responder was defined as "normal" vaginal discharge, negative "whiff" test, and clue cells <20%. Additional endpoints included Nugent score cure (Nugent score of 0-3) and therapeutic outcome. A therapeutic responder was defined as a clinical responder with a Nugent score cure. In Trial 2, the endpoints were also assessed at Day 7-14. In both trials, a statistically significantly greater percentage of patients experienced clinical response, Nugent score cure, and therapeutic response at 21 to 30 days following a single dose of Solosec compared to placebo. Statistically significant results for the endpoints were also achieved at Day 7-14 in Trial 2. The percentage of patients with clinical response was also consistently higher in both trials in the

Solosec arm compared to placebo among all subsets of patients: number of prior episodes of bacterial vaginosis (≤ 3 episodes and ≥ 4 episodes) in past 12 months, baseline Nugent score (score 4-6 and score 7-10), and race (Black/African American and White). Tables 2 and 3 describe the efficacy of Solosec in the treatment of bacterial vaginosis.

Table 2 Efficacy of Solosec for Treatment of Bacterial Vaginosis in Two Randomized, Double-Blind, Placebo-Controlled Trials in Modified-Intent-to-Treat Population at 21-30 Days.

	Trial 1		Trial 2	
	SOLOSEC (N=62)* n (%)	Placebo (N=62) * n (%)	SOLOSEC (N=107)* n (%)	Placebo (N=57) * n (%)
Clinical Responder†	42 (67.7)	11 (17.7)	57 (53.3)	11 (19.3)
	50.0 (33.4, 66.7)‡ p<0.001		34.0 (18.7, 49.3) ‡ p<0.001	
Nugent Score Cure§	25 (40.3)	4 (6.5)	47 (43.9)	3 (5.3)
	33.8 (18.5, 49.1) ‡ p<0.001		38.6 (26.2, 51.0) ‡ p<0.001	
Therapeutic Responder	25 (40.3)	4 (6.5)	37 (34.6)	2 (3.5)
	33.8 (18.5, 49.1) ‡ p<0.001		31.1 (19.6, 42.6) ‡ p<0.001	

*N=number of patients in treatment group (modified intent-to-treat population defined as all patients randomized who had a baseline Nugent score ≥4 and were negative for other sexually transmitted infections at baseline). †Patients missing one or more of the clinical assessments were considered as non-responders/not cured. ‡Difference in response (SOLOSEC – placebo) and 95% confidence interval §Patients with missing Nugent scores were considered Nugent score failures
Source: Solosec Package Insert, Appendix A

Table 3 Efficacy of Solosec for Treatment of Bacterial Vaginosis in Trial 2 in Modified Intent-to-Treat Population at 7-14 Days

	Trial 2	
	SOLOSEC (N=107) * n (%)	Placebo (N=57) * n (%)
Clinical Responder†	62 (57.9)	14 (24.6)
	33.3 (17.4, 49.2) ‡ p<0.001	
Nugent Score Cure§	49 (45.8)	2 (3.5)
	42.3 (30.4, 54.2) ‡ p<0.001	
Therapeutic Responder	37 (34.6)	2 (3.5)
	31.1 (19.6, 42.6) ‡ p<0.001	

*N=number of patients in treatment group (modified intent-to-treat population defined as all patients randomized who had a baseline Nugent score ≥4 and were negative for other sexually transmitted infections at baseline). †Patients missing one or more of the clinical assessments were considered as non-responders/not cured. ‡Difference in response (SOLOSEC – placebo) and 95% confidence interval §Patients with missing Nugent scores were considered Nugent score failures
Source: Solosec Package Insert, Appendix A

4. STUDY OBJECTIVES

4.1 PRIMARY OBJECTIVE(S)

The objective of this study is to evaluate safety of single oral dose of Solosec™ (secnidazole) 2g oral granules for the treatment of adolescent girls with bacterial vaginosis.

4.2 SECONDARY OBJECTIVE(S)

Secondary assessments of efficacy will be assessed.

4.3 STUDY ENDPOINTS

4.3.1 Efficacy Endpoints

Although this study is primarily an observational safety study, some efficacy endpoints will be evaluated at the TOC Visit (Study Day 7-14) including:

- Clinical Outcome: A Clinical Outcome Responder is defined as a patient with all of the following:
  1) Resolution of abnormal vaginal discharge, and
  2) Negative 10% KOH Whiff test; and
  3) Clue cells less than 20% of the total epithelial cells on microscopic examination of the vaginal wet mount using saline.
- Nugent Score - TOC Visit [Study Day 7-14] score of 0-3 will be considered normal; a score of 4 and above will be considered abnormal.
- Investigator's Clinical Assessment - TOC Visit [Study Day 7-14]: Investigator's opinion of the need for additional BV treatment (Yes or No).
- Patient's Continued Clinical Response - Study Day 21-30 only: Investigator's opinion of the continued clinical response to treatment (Yes or No)

4.3.2 Safety Endpoints

Safety endpoints include:

- Adverse events (AEs): Includes treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), treatment-related AEs, and AEs leading to study discontinuation.
- Vital signs: Blood pressure, temperature and pulse.
- Physical Examinations:
- Pelvic Examinations: External genitalia and vagina
- Laboratory assessments: Includes serum chemistry, hematology and urinalysis

5. STUDY DESIGN

5.1 OVERALL STUDY DESIGN

This is a multi-center, open-label study to evaluate the safety of Solosec in adolescent girls with bacterial vaginosis. Approximately 40 patients will be enrolled. Patients determined to be eligible at the Baseline Visit (Day 1) will receive a single oral dose of Solosec™ granules (containing 2g of secnidazole) on Day 1. Patients will return to the site once between Days 7-14 for a "test of cure" (TOC) Visit. A follow-up telephone call will be performed at Days 21-30 to assess the continued clinical response to treatment and adverse events (See Schedule of Assessments table for a complete list and timing of assessments and tests).

5.2 DOSE RATIONALE

Solosec (secnidazole) 2g oral granules is a FDA approved treatment for bacterial vaginosis (BV) in adult women. Solosec is a potent, 5-nitroimidazole antibiotic with enhanced pharmacokinetic properties that enable delivery in a single dose that has been shown to be efficacious and well tolerated.

6. SELECTION AND WITHDRAWAL OF SUBJECTS

Approximately 40 patients will be enrolled.

6.1 INCLUSION CRITERIA

A subject will be eligible for enrollment if all of the following inclusion criteria apply:

1. Are adolescent girls 12-17 years of age.
2. Are willing and able to give written informed assent with a written informed consent from a parent or legal guardian.
3. Are in good general health including as confirmed by a medical history and physical examination, with no known medical or mental health conditions that, in the Investigator's opinion, may interfere with study participation.
4. Willing and able to participate in the study as an outpatient, make required visits to the study center, and comply with all study requirements.
5. Have a negative urine pregnancy test result prior to study treatment initiation. In addition, female patients of childbearing potential must be using an acceptable form of birth control as determined by the Investigator (e.g., oral contraception, implantable, injectable or transdermal hormonal contraception, intrauterine device [IUD], double-barrier methods, have a vasectomized partner or abstinence [if the patient becomes sexually active they must use one of the acceptable methods of birth control]). Note: NuvaRing® or any other vaginal ring products are not permitted.
6. Have a clinical diagnosis of bacterial vaginosis, defined as having all of the following criteria:
    a. Off-white (milky or gray), thin, homogeneous vaginal discharge AND
    b. Vaginal pH > 4.5 AND
    c. Presence of Clue cells of ≥ 20% of the total epithelial cells on microscopic examination of the vaginal saline wet mount AND
    d. A positive 10% KOH Whiff test.
7. Agree to abstain from vaginal intercourse until after the TOC visit.
8. Agree not to have any vaginal penetration or use of any vaginal products until after the TOC visit (e.g., spermicides, condoms, diaphragms, vibrators, tampons, etc.).
9. Agree not to use vaginal douches or similar products for the duration of the study.

6.2 EXCLUSION CRITERIA

A subject who meets any of the following exclusion criteria must not be enrolled:

1. Are pregnant, lactating, or planning to become pregnant during the study.
2. Are menstruating or have vaginal bleeding at the Baseline Visit (Day 1).

3. Are menopausal as determined by the Investigator.
4. Are suspected clinically (or confirmed diagnostically) of having alternative causes of vaginal symptoms including candidiasis, *Chlamydia trachomatis, Trichomonas vaginalis, Neisseria gonorrhoeae* or Herpes simplex or human papilloma virus.
5. Have active genital lesions, including active Herpes simplex lesions, or other vaginal or vulvar conditions which could confound the interpretation of the clinical response, as determined by the Investigator (patients with genital warts that are not being treated may be enrolled).
6. Have received antifungal or antimicrobial therapy (systemic or intravaginal) within 14 days prior to the Baseline Visit (Day 1).
7. Are using NuvaRing® or any other vaginal ring products.
8. Have consumed any alcohol within 12 hours prior to treatment with study medication.
9. Have a history of drug or alcohol abuse within the past 6 months, as determined by the Investigator.
10. Have participated in any investigational trial within 30 days or six half-lives of the test drug's biologic activity, whichever is longer, before the Baseline Visit (Day 1).
11. Are participating in any investigational, observational or non-interventional study (either currently or during the study).
12. Have had previous exposure to SYM-1219 or participation in other clinical trials of SYM-1219.
13. Have a known allergy to nitroimidazoles (e.g., metronidazole, tinidazole, nimorazole, etc.).
14. Have a history of an abnormal Pap smear which required cervical biopsy or cervical cauterization within 3 months of the Baseline Visit (Day 1).
15. Have any history of cervical carcinoma or other carcinomas of the vagina or vulva.
16. Have any condition that interferes with their ability to understand or comply with the requirements of the study.

6.3 RANDOMIZATION CRITERIA

Subjects that meet all Inclusion/Exclusion criteria listed above will be enrolled in this open-label study. Upon approval by the medical monitor and sponsor, subjects who do not qualify based on a reversible medical condition or mild intercurrent illness may be re-evaluated after further testing/examination or re-screened after the condition is resolved.

6.4 WITHDRAWAL CRITERIA

Patients may withdraw from the study at any time and for any reason. Reasons for discontinuation include, but are not limited to, the following:

- Investigator's request
- Safety reasons (e.g., adverse event); any AEs continuing at the time of withdrawal should be followed until resolution or determined by the Investigator to be chronic or stable
- Patient's request
- Perceived lack of therapeutic effect
- Sponsor's or CRO's request
- Positive for STIs from samples obtained at Baseline Visit (Day 1)
- Non-compliance with study protocol as determined by the Investigator or Sponsor
- Patient's use of, or need for, concomitant therapy liable to interfere with the interpretation of study endpoints. The Investigator will report all such information on the electronic Case Report Form (eCRF) and decide, in accordance with the Medical Monitor, whether the patient should be withdrawn from the study.
- Patient lost to follow-up. The Investigator will try to reach the patient, twice by telephone and once by certified letter, before considering the patient lost-to-follow-up. These actions will be reported on the appropriate source documents, and a copy of the certified letter will be maintained in the Investigator's file.

All premature discontinuations and their causes must be documented by the Investigator on the appropriate eCRF page, and if need be, on the Adverse Event page of the eCRF.

Patients who are prematurely discontinued from study after enrollment due to positive STIs from samples obtained at the Baseline Visit (Day 1) should have all End of Study (EOS) Visit procedures performed.

Patients not completing the entire study should be fully evaluated (i.e., final visit procedures performed), wherever possible.

All patients are free to withdraw from participating in this study at any time and for whatever reason, specified or unspecified, and without prejudice to her medical care.

Subjects may withdraw consent and/or may be discontinued by the investigator or Sponsor for any reason at any time.

A subject may withdraw or be withdrawn for any of the following reasons:

6.5 REPLACEMENT OF SUBJECTS WHO WITHDRAW OR ARE DISCONTINUED

Subjects who withdraw, are discontinued, or are lost to follow-up may be replaced upon review/approval from the Sponsor.

The date the subject is withdrawn from the study and the reason for discontinuation will be recorded in the CRF. If there are multiple reasons for early discontinuation, the worst-case scenario should be chosen.

If a subject is withdrawn because of an adverse event, the event will be followed until the medical condition returns to baseline or is considered stable or chronic. Discontinuation of subjects due to adverse events, including those due to abnormal laboratory results, should be promptly reported to Sponsor.

7. TREATMENTS

Marketed Solosec will be utilized.

7.1 TREATMENTS ADMINISTERED

All patients enrolled in the study will receive a single oral dose of Solosec™ granules (containing 2g of secnidazole) on Day 1.

7.2 SUPPLY OF STUDY MEDICATION

Solosec will be provided by the sponsor.

7.3 BLINDING

This is an open-label study.

7.4 DOSING PROCEDURES

Study drug will be orally administered as a single dose with 4 ounces of unsweetened applesauce (Mott's® applesauce, a spoon, and an 8 ounce bottle of water will be included in the treatment kits). The study medication will be mixed and administered by the study patient on Day 1, without regard to meals. After taking the dose of study medication, the patient will be instructed to drink approximately 8 ounces of water.

7.5 STUDY MEDICATION ACCOUNTABILITY

Each study center is to use a study drug accountability log to document study drug disposition. All items on this form are to be completed in full.

The investigator identification number and patient initials and identification number are to be recorded on each study drug accountability log. Each time study personnel dispenses study drug for a patient, he or she is to record the date dispensed, and his or her initials. Study personnel are to monitor the inventory of clinical supplies and maintain a count of all used and unused study drug. The CRA is to review study drug accountability records and remaining drug supplies during routine monitoring visits.

8. PROHIBITED AND RESTRICTED MEDICATIONS AND PROCEDURES

All prescription and non-prescription medications and therapies, including vitamins, herbal medicines, or other non-traditional medicines, taken from 30 days prior to the first study drug dose through the end of the study must be recorded in the eCRF.

The following medications and products are prohibited during study participation, as described below:

- Systemic antimicrobial therapies for the duration of the study, with the exception of oral antifungal therapy (e.g., oral fluconazole) to treat intercurrent conditions (e.g., vulvovaginal candidiasis);
- Topical antimicrobial/ antifungal / immunomodulatory therapies in the genital area (vagina, vulva and surrounding soft tissue), including treatments for external genital warts;
- Warfarin;
- Systemic corticosteroids (intranasal and inhaled steroids are permitted).

8.1 DIET, FLUID, AND ACTIVITY CONTROL

The following products are restricted during study participation, as described below:

- Patients should not have vaginal intercourse until after the TOC visit.
- Patients should not have any vaginal penetration or use any vaginal products until after the TOC visit (e.g., spermicides, condoms, diaphragms, vibrators, tampons, etc.);
- Patients should not use vaginal douches or similar products for the duration of the study.

9. STUDY CONDUCT

9.1 OVERVIEW

The time and events schedule for the study is presented in Table 1, Schedule of Assessments.

9.2 STUDY PROCEDURES

Patients will be scheduled to visit the clinic two times during the study (Baseline Visit and TOC/EOS Visit on Days 7-14). A telephone interview will be performed on Days 21-30.

9.3 STUDY VISITS

9.3.1 Baseline Visit (Study Day 1)

The following procedures should be completed prior to initiating study treatment:

1. Obtain a signed and dated patient informed consent form/Authorization to disclose Health Information/assent and authorization to use and disclose medical information prior to performing any study-specific procedures;
2. Collect demographic information including date of birth, sex, race, and ethnicity;
3. Collect a medical history;
4. Collect BV history and prior treatments;
5. Collect prior and concomitant medication use;
6. Perform a urine pregnancy test;
7. Perform a physical exam, including vital signs, weight and height;
8. Perform a pelvic examination including examination of the internal and external genitalia and a bimanual examination and assess vaginal discharge and collect vaginal samples as follows:
    a. Examine the external genitalia and vagina;
    b. Observe for presence of off-white (milky or gray), thin, homogeneous discharge;
    c. OSOM® Trichomonas Rapid Test;
    d. Vaginal saline wet mount for assessment of Clue cells, fungal elements, and trichomonads;
    e. Vaginal sample for Gram stain (slide sent to central laboratory for Nugent Scoring - results will not be available at the time of randomization);
    f. 10% KOH whiff test and review of slide for fungal elements;
    g. pH of vaginal fluid;
    h. Sexually transmitted infections (STIs) Assessments (*Neisseria gonorrhoeae*, *Trichomonas vaginalis* and *Chlamydia trachomatis* (swabs of

vaginal fluid sent to central laboratory; results will not be available at time of enrollment);

i. A bimanual pelvic examination will be performed after completion of the procedures above.

9. Collect blood and urine samples for analysis at the central laboratory (results will not be available at time of enrollment);
10. Review inclusion and exclusion criteria.

If the patient meets all clinically available inclusion/exclusion criteria, the site will enroll the patient into the study. The following procedures will be performed after the patient has been enrolled:

1. The patient self-administered the study medication (without regard to meals). After taking the dose of study medication, the patient was instructed to drink approximately 8 ounces of water.
2. Schedule the TOC/EOS clinic Visit between Study Day 7-14.

Patients with baseline laboratory results that are determined to be positive for *Neisseria gonorrhoeae*, *Trichomonas vaginalis* and/or *Chlamydia trachomatis* after study enrollment will be contacted and scheduled for an EOS Visit as soon as possible, and discharged from the study. Patients who are subsequently found to have a normal Nugent Score from the sample obtained at the Baseline Visit (Study Day 1) (Nugent Score between 0-3) should remain in the study and complete all study visits for safety data collection. Nugent Score results will also be used as one of the criteria for determining analysis populations.

9.3.2 Test of Cure Visit (Study Day 7-14) / End of Study (EOS) Visit

The Test of Cure (TOC) / End of Study (EOS) Visit should be conducted between Study Day 7 and 14. The TOC/EOS visit should not be scheduled during the patient's menses. If a patient requires early termination (including for a positive STI result from samples obtained at the Baseline Visit [Day 1]), or if the TOC Visit cannot be conducted between Study Day 7-14, the patient should be scheduled for an EOS Visit with all procedures performed.

The following procedures will be performed at the TOC/EOS Visit:

1. Assess for adverse events;
2. Review and record concomitant medications/treatments taken during the study;
3. Perform a urine pregnancy test;
4. Perform a targeted physical examination as needed to assess AEs. Collect vital signs;
5. Perform a pelvic examination, including examination of the internal and external genitalia, and assess the vaginal discharge, and collect vaginal samples as follows:
   a. Examine the external genitalia and vagina;
   b. Assess if patient's vaginal discharge is normal or abnormal;

c. Vaginal saline wet mount for assessment of Clue cells, fungal elements, and trichomonads;

d. Vaginal sample for Gram stain and Nugent scoring;

e. 10% KOH Whiff test and review of slide for fungal elements;

f. STI Assessments (*Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Trichomonas vaginalis*) only if clinically indicated as determined by the Investigator);

g. At the Investigator's discretion, a bimanual pelvic examination may be performed after completion of the procedures above.

6. Collect blood and urine samples for analysis at the central laboratory;
7. Investigator's assessment for the need of additional treatment for BV.

9.3.3 Patient Telephone Interview (Study Day 21-30)

The patient telephone interview should be conducted between Study Day 21 and 30.

The following information should be collected:

1. Assess for adverse events;
2. Review and record concomitant medications/treatments.
3. Conduct telephone interview (see section 9.7).

9.4 METHODS OF ASSESSMENTS

9.4.1 Demographics

Patient demographics, including age, sex, race, and ethnicity, are to be documented during screening.

9.4.2 Patient Medical History

A complete medical history is to be documented at the Baseline Visit (Day 1) (including the number of reported episodes of BV in the past 12 months, inclusive of the current episode).

9.4.3 Vital Signs

Vital signs, including seated systolic and diastolic blood pressure (mm Hg), pulse (beats per minute), and temperature are to be measured for all patients at the Baseline Visit (Day 1) predose, and at the TOC/EOS Visit.

Blood pressure (BP) and pulse will be measured using a BP recording device with an appropriate cuff size.

If an abnormality is considered by the Investigator to be clinically significant, then the abnormality is to be recorded as part of the patient's medical history if occurring prior to start of study drug administration and as an adverse event if occurring after any study drug administration, where the finding represents a change from the Baseline Visit (Day 1).

9.4.4 Urine Pregnancy Testing

An in-office urine pregnancy test must be performed for all patients at the Baseline Visit (Day 1) and TOC/EOS Visit (Days 7-14). Patients must have a negative urine pregnancy test at the Baseline Visit prior to enrollment. Urine pregnancy testing should also be conducted at an unscheduled visit for any patient who is suspected of being pregnant (additional pregnancy testing may be conducted at the Investigator's discretion).

9.4.5 Physical Examination, Height, and Weight

A physical examination which includes examination of head, eyes, ears, nose, and throat (HEENT); neck; cardiovascular; lungs; abdomen; extremities; skin; lymph nodes; and musculoskeleton, will be conducted for all patients during the Baseline Visit (Day 1). Height and weight are to be measured at the Baseline Visit. A targeted physical examination at the TOC/EOS Visit is only needed per the Investigator's discretion if a reported AE requires further evaluation.

9.4.6 Pelvic Examination, Vaginal Discharge Assessment and Testing

A pelvic examination (including examination of the internal and external genitalia), vaginal discharge assessment and testing will be performed at the Baseline Visit (Day 1) and TOC/EOS Visit and at any time during the study if the patient's clinical response is perceived to be inadequate or as dictated by patient symptoms. A non-lubricated speculum must be used during the pelvic examination. Components of the pelvic examination are specified in the following sections. It is recommended that the vaginal sample for the OSOM® Trichomonas Rapid Test be obtained early in the collection process to ensure adequate sample for this evaluation. A bimanual pelvic examination will be performed after the vaginal discharge assessment has been performed and all the vaginal samples have been collected at the Baseline Visit. At the TOC/EOS Visit, at the Investigator's discretion, a bimanual pelvic examination may be performed after the vaginal discharge assessment has been performed and all vaginal samples have been collected.

Prior to enrollment, if any test result is considered exclusionary it is not required to complete the evaluation of any additional samples. Therefore, these patients should be immediately discharged; no blood samples should be drawn and vaginal samples should not be shipped for laboratory testing.

9.4.7 Examination of External Genitalia and Vagina

An examination of the external genitalia and vagina will be performed and recorded as normal or abnormal.

9.4.8 Vaginal Discharge Assessment

During the pelvic examination, observe for presence of off-white (milky or gray), thin, homogeneous discharge (record as Normal, Abnormal consistent with [BV], or Abnormal Other).

9.4.9 Vaginal Discharge Testing

9.4.9.1 *Preparation of Slides for Vaginal Saline Wet Mount and Whiff Test*

Using sterile polyester-tipped swabs, swab the lateral vaginal walls with a polyester -tipped applicator and place polyester tip in a tube with approximately 6 drops of saline (~100 µl; enough to keep the swab moist, but not dilute the sample). Remove the swab from the tube and place a liberal amount of discharge on each of the two glass slides immediately before testing as follows:

9.4.9.1.1 *Slide #1 – KOH Whiff Test*

The Investigator, or designee, will mix approximately two drops of 10% potassium hydroxide (KOH) with the vaginal discharge sample and immediately smell the slide (Note: the assessor should not have any impairment to the sense of smell).

- Assess for a fishy, amine-like odor (record as Positive or Negative; note that a Positive result indicates the presence of the odor). A positive 10% KOH Whiff test is required for study enrollment.
- Coverslip the slide.
- Under a light microscope at 100X magnification, examine the entire coverslipped area for the presence of fungal elements (e.g., budding yeast or hyphae/pseudohyphae). If found, confirm the identification at 400X magnification. If fungal elements are confirmed, the patient will be excluded from the study.

9.4.9.1.2 *Slide #2 –Vaginal Saline Wet Mount*

The Investigator, or designee, will examine the second vaginal sample slide under a light microscope at 100X magnification and at 400X magnification. Examine for the presence or absence of Clue cells, motile trichomonads, and fungal elements.

- **Clue cells:** A minimum of 5 representative fields containing squamous epithelial cells should be examined and the ratio of Clue cells to vaginal epithelial cells determined at 400X magnification. Clue cells will be identified as vaginal epithelial cells with such a heavy coating of bacteria surrounding them their peripheral borders are obscured. The presence of Clue cells of $\geq$ 20% of the total epithelial cells on microscopic examination of the vaginal saline wet mount are required for inclusion at the Baseline Visit (Day 1). Record Clue cells as $\geq$ 20% of the total epithelial cells, or $<$ 20% of the total epithelial cells.
- **Trichomonads:** Record as Present or Absent. If mobile trichomonads are visible on the slide, the patient has a diagnosis of trichomoniasis and is therefore excluded from the study.
- **Fungal elements:** Record as Present or Absent. It is possible that the presence of fungal elements may be observed under 100X magnification. If found, confirm the identification at 400X magnification. If fungal elements are confirmed, the patient will be excluded from the study.

9.4.9.2 *Preparation of Vaginal Smear for Gram Stain/Nugent Scoring*

A vaginal sample will be obtained by the Investigator, or designee, for the preparation of two slides (one primary and one backup slide) for both Gram staining and Nugent scoring at the central laboratory (Magee-Womens Research Institute, Pittsburgh, PA). The slides will be prepared as follows:

1. Label with pencil both frosted-ended slides with the protocol number, patient number, study visit (Baseline, TOC/EOS), and date collected.
2. Rotate the sterile polyester-tipped swab over the lateral vaginal wall approximately 5 times. Do not swab too close to the cervix.
3. Roll the swab gently on each slide to make a thin even smear.
4. Allow the slides to air dry.
5. Place each slide in a slide holder.
6. Place a study label on the outside of each holder.
7. Store at room temperature.
8. Ship slide(s) to Magee-Womens Research Institute according to instructions provided in the laboratory manual. The Nugent Score results will not be available at the time of randomization (the patient may be randomized without these results). The patient will remain in the study regardless of the Nugent Score results; however, the results will be used as one of the criteria for analysis.

9.4.9.3 *Vaginal pH*

The pH of a vaginal sample will be obtained by the Investigator, or designee, at the Baseline Visit (Day 1) only, and the result will be recorded (recorded as > 4.5 or ≤ 4.5). If the pH is ≤ 4.5 at Baseline, the patient cannot be enrolled into the study. The necessary materials and instructions will be provided for vaginal pH testing (refer to laboratory manual for instructions).

9.4.9.4 *Sexually-transmitted Infection Assessments*

Assessments for the presence of the following sexually-transmitted infections (STIs) will be performed at the Baseline Visit (Day 1) and only if clinically indicated at TOC/EOS Visit (or unscheduled visits).

9.4.9.4.1 *Neisseria gonorrhoeae*

A vaginal sample will be obtained and sent to the central laboratory for *Neisseria gonorrhoeae* testing (refer to laboratory manual for instructions). The *Neisseria gonorrhoeae* testing results from the central laboratory will not be available at the time of enrollment (the patient may be enrolled without these results). If the Baseline Visit (Day 1) sample is subsequently positive for this test, the patient should be discontinued from the study and directed to appropriate treatment.

9.4.9.4.2 *Chlamydia trachomatis*

A vaginal sample will be obtained and sent to the central laboratory for *Chlamydia trachomatis* testing (refer to laboratory manual for instructions). The *Chlamydia*

trachomatis testing results from the central laboratory will not be available at the time of enrollment (the patient may be enrolled without these results). If the Baseline Visit (Day 1) sample is subsequently positive for this test, the patient should be discontinued from the study and directed to appropriate treatment.

9.4.9.4.3 *Trichomonas vaginalis*

The presence or absence of *Trichomonas vaginalis* will be determined by the Investigator, or designee using the OSOM® Trichomonas Rapid Test. Commercial test kits will be provided to the sites, and testing will be performed as described in the test instructions (refer to laboratory manual for instructions). Record as Positive or Negative; note that a Positive result indicates the presence of *Trichomonas vaginalis*; therefore, the patient must not be enrolled into the study. Note: it is recommended that the vaginal sample for the OSOM® Trichomonas Rapid Test be obtained early in the collection process to ensure adequate sample for this evaluation. Additionally, the presence of *Trichomonas vaginalis* may be determined by microscopy at the investigative site during review of the vaginal saline wet mount slide.

Additionally, a vaginal sample will be obtained and sent to the central laboratory for *Trichomonas vaginalis* TMA testing (refer to laboratory manual for instructions). If the Baseline Visit (Day 1) sample is subsequently positive for this test, the patient should be discontinued from the study and directed to appropriate treatment.

9.4.10 Bimanual Pelvic Examination

A bimanual pelvic exam will be performed after the vaginal discharge assessment and all the vaginal samples have been collected at the Baseline Visit. At the Investigator's discretion, a bimanual examination may be performed after assessment of vaginal discharge and all of the vaginal samples have been collected at the TOC/EOS Visit. If performed, the findings will be recorded in the eCRF.

9.5 CLINICAL LABORATORY ASSESSMENTS

Clinical laboratory safety assessments will be performed by a central laboratory and results will not be available until after the patient has been enrolled.

If an abnormality is considered by the Investigator to be clinically significant, then the abnormality is to be recorded as part of the patient's medical history if occurring prior to start of study drug administration and as an adverse event if occurring after any study drug administration, where the finding represents a change from the Baseline Visit (Day 1).

9.5.1 Safety Laboratory Tests

Blood and urine for safety laboratory tests are to be collected from all patients at the Baseline Visit (Day 1) and at the TOC/EOS Visit.

At each time point, the following parameters are to be measured:

Hematology	**Chemistry**	**Urinalysis**
WBC with differential:	Chloride	Appearance
(% & absolute)	Carbon dioxide (CO_2)	Specific gravity
• Basophils	Potassium	pH
• Eosinophils	Sodium	Protein
• Lymphocytes	Blood urea nitrogen	Glucose
• Monocytes	Calcium	Ketones
• Neutrophils	Creatinine	Blood
Red Blood Cells (RBC)	Glucose	Leukocyte esterase
Hemoglobin	Albumin	Nitrite
Hematocrit	Alkaline phosphatase	Bilirubin
Platelet count	Aspartate aminotransferase (AST)	Urobilinogen
Red cell indices	Aspartate transaminase (ALT)	Microscopy
	Total bilirubin plus direct and indirect	
	Total protein	

9.6 INVESTIGATOR'S CLINICAL ASSESSMENT

The Investigator will answer the following question at the TOC/EOS Visit: "In your opinion, does the patient require additional treatment for bacterial vaginosis infection at this time? The response will be recorded as Yes or No. If the answer is Yes, the patient will be offered a prescription for a post-study treatment by the Investigator.

9.7 TELEPHONE INTERVIEW OF PATIENT

A telephone interview will be performed with the subject between 21 to 30 days after enrollment. The Investigator will assess the continued clinical response to treatment and adverse events. Based on the subject interview, the Investigator will answer the following question "In your opinion, is there a continued clinical response with Solosec at this time?" The response will be recorded as Yes or No.

10. SAFETY AND PHARMACOVIGILANCE

10.1 DEFINITION OF AN ADVERSE EVENT

An adverse event (AE) is defined as any untoward medical occurrence in a clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with the treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product.

A new condition or the worsening of a pre-existing condition will be considered an AE. Stable chronic conditions such as arthritis that is present prior to study entry and do not worsen during the study will not be considered AEs. Worsening of the disease under study should only be recorded as an AE if the outcome is more serious than would normally be expected from the normal course of the disease in a particular subject.

An abnormal result of diagnostic procedures including abnormal laboratory findings will be considered an AE if it:

- Results in subject's withdrawal by the investigator
- Is associated with a serious adverse event (SAE)
- Is associated with clinical signs or symptoms
- Is considered by the physician to be of clinical significance

Unlabeled/Unexpected AE - A reaction which is not included in the Adverse Reaction section of the relevant Reference Safety Information by its **specificity, severity, outcome, or frequency. The labeling reference for this study is the Approved Label (Appendix A).**

In the study, any event occurring after the clinical trial subject has signed the study Informed Consent (ICF) should be recorded and reported as an AE. Those events occurring prior to enrollment will be considered to be "Non-Treatment-Emergent" AEs and those occurring post-enrollment as "Treatment-Emergent" AEs.

10.2 INTENSITY OF ADVERSE EVENTS

The intensity or severity of the AE will be characterized as:

- **Mild**: AE which is easily tolerated
- **Moderate**: AE sufficiently discomforting to interfere with daily activity
- **Severe**: AE which prevents normal daily activities

When the intensity of an adverse event changes more than once a day, the maximum severity for the event should be listed. If the intensity changes over a number of days, these mini-events or changes should be recorded separately (i.e., having distinct onset dates).

10.3 RELATIONSHIP OF ADVERSE EVENTS TO STUDY DRUG

The causal relationship of the investigational product to the AE(s) should be characterized as:

Not Related: There is *no reasonable possibility* that the AE was caused by or attributed to the investigational product

Related: There is a *reasonable possibility* that the AE was caused by or attributed to the investigational product. A causal relationship cannot be ruled out.

10.3.1 Definition of "No Reasonable Possibility"

The assessment term, "*no reasonable possibility*", can only be applied to those AEs which, after careful consideration, are clearly due to extraneous causes (disease, environment, etc.) or to those AEs which, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the study drug.

An AE may be considered as being meeting the definition of "no reasonable possibility" if it is clearly due to extraneous causes or when at least two of the following applies:

- It does not follow a reasonable temporal sequence from the administration of the study drug
- It could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject
- It does not follow a known pattern of response to the study drug
- It does not reappear or worsen when the drug is re-administered.

10.3.2 Definition of "Reasonable Possibility"

The assessment term, "*reasonable possibility*", can only be applied to those AEs which, after careful medical consideration at the time they are evaluated, a connection with the study drug administration cannot be ruled out with certainty or is felt with a high degree of certainty to be related to the study drug.

An AE may be considered as meeting the definition of "reasonable possibility" if or when at least two of the following applies:

- It follows a reasonable temporal sequence from the administration of the study drug
- It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject
- It disappears or decreases on cessation or reduction in dose. There are important exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists.
- It follows a known pattern of response to the study drug.

10.4 RECORDING OF ADVERSE EVENTS

Adverse Events are illnesses or signs/symptoms that appear or worsen during the testing of a drug whether or not considered related to the investigational product (synonyms = medicinal or pharmaceutical product, study drug, clinical trial materials, etc.), including side effects, injury, toxicity, or hypersensitivity reactions.

All adverse events, including observed, elicited, or volunteered problems, complaints or symptoms, are to be recorded on the Adverse Events page in the subject's Case Report Form.

The need to capture this information is not dependent upon whether adverse events are associated with use of the investigational product.

Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications progression of disease states should also be recorded. In order to avoid vague, ambiguous or colloquial expressions, adverse events should be recorded in standard medical terminology rather than the subject's own words. Signs and symptoms should be reported individually unless, in the judgment of the investigator, they can be grouped under an inclusive term (e.g., gastroenteritis in lieu of abdominal pain, nausea, vomiting, and diarrhea).

Each adverse event is to be evaluated for date/time of onset, duration, intensity, and causal relationship with the investigational product or other factors.

At every study visit, the investigator must document new AEs and the outcome of ongoing AEs. Any subject with an AE (including SAEs) or any clinically significant abnormal laboratory result or physical finding reported as an AE will be followed by the investigator until the AE resolves, resolves with sequalae, is otherwise explained by a medical condition, follow-up is not possible (document), or the subject dies.

10.5 DEFINITION OF A SERIOUS ADVERSE EVENT

A Serious Adverse Event (SAE) is defined as an AE that results in any of the following:

- Death
- Life-threatening
- Requires hospitalization or prolongs existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- An important medical event which requires medical intervention to prevent any of the above outcomes

Important medical events are those which may not be immediately life-threatening, but may jeopardize the subject and may require intervention to prevent one of the other serious outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; resulting in an adverse event will normally be considered serious by this criterion.

Inpatient **hospitalization** or prolongation of existing hospitalization means that hospital inpatient admission and/or prolongation of hospital stay were required for

treatment of AE, or that they occurred as a consequence of the event. It does not refer to pre-planned elective hospital admission for treatment of a pre-existing condition that has not significantly worsened, or to diagnostic procedures.

The term **"life-threatening"** in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

The term "**disability"** in the definition of "serious" refers to an event in which the subject's ability to conduct normal life functions was substantially disrupted.

Severe vs. Serious AEs: The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe headache). This is not the same as "serious", which is based on subject/event outcome or reaction criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Any new SAE that occurs after the study period and that is considered to be related (possibly/probably) to the study drug or study participation should be recorded and reported immediately (Section 10.6). The study period for the purpose of SAE reporting is defined as the period from the subject's signature on the informed consent form until the end of the protocol-defined follow-up visit/period.

10.6 SERIOUS ADVERSE EVENT REPORTING

In order to satisfy regulatory requirements, any Serious Adverse Event, whether deemed study drug-related or not, must be reported to the Sponsor's Local Clinical Management (LCM) or designee as soon as possible after the investigator or site coordinator has become aware of its occurrence. The SAE form completion and reporting must not be delayed even if all of the information is not available at the time of the initial contact.

The LCM contact for this study is:

Dr Deepa Arora
Lupin Ltd,
Kalpataru Inspire, 5th Floor, Santacruz (E),Mumbai -400055, India
Ph No.: +91-22-66402348
Mobile No.: 91-9820648395
Email: deepaarora@lupin.com

The Medical Monitor for this study is:

Sharon Levy, MD
996 Old Eagle School Rd., Suite 1106
Wayne, PA19087
Phone: 484-320-2062
Email: s.levy@prosoftclinical.com

Serious Adverse Events: Email - LupinSAEreporting@prosoftclinical.com

The SAE should be submitted within 24 hours of becoming aware of the event to the Sponsor's LCM or designee. LCM or designee will forward the SAE report to the Sponsor's pharmacovigilance unit.

Additional information (follow-up) about any SAE unavailable at the initial reporting should be forwarded by the site within 24 hours of the information becoming available to the LCM or designee.

In non-EU countries, serious adverse events should be reported by the site to their local IRB/IEC as dictated by their board's policies and procedures.

Subjects who have had an SAE during the treatment period must be followed clinically until all parameters (including laboratory) have either returned to normal or have stabilized or are otherwise explained.

Any newly emergent SAEs after treatment is discontinued or the subject has completed the study and is considered to be related to the study drug or study participation should be recorded and reported immediately. The post-study period for the purpose of SAE reporting is routinely for up to 30 days following last visit of the study or until SAE is resolved or stabilized.

Pregnancy reports: Pregnancy alone is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. Elective abortions without complications should not be handled as AEs, unless they were therapeutic abortions. Hospitalization for normal delivery of a healthy new born should not be considered an SAE.

Pregnancies occurring during the study until EOS must be reported. All pregnancies must be reported to the sponsor within 24 hours after becoming aware of the pregnancy, using the initial pregnancy report form. The investigator should counsel the patient; discuss the risks of continuing with the pregnancy and possible effects on the fetus. The investigator must follow up and document the course and outcome of all pregnancies, even if the patient was discontinued from the study or if the study has finished.

All outcomes of pregnancy must be reported by the investigator to the sponsor on the pregnancy outcome report form within 30 days after he/ she becomes aware of the outcome. Any SAE that occurs during a pregnancy must be recorded on the SAE report form (e.g. maternal serious complications, spontaneous or therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, or birth defects) and reported in accordance with the procedure for reporting of SAEs.

10.7 REPORTING TO THE UNITED STATES FOOD AND DRUG ADMINISTRATION (US FDA)

The sponsor will report expeditiously all Serious and Unexpected Suspected Adverse Reaction to the USFDA, Investigators & IRB's as IND Safety Report according to 21 CFR 312 regulations

11. DATA COLLECTION AND ANALYSIS

This section describes the biostatistical analysis as foreseen at the time of planning the study. Changes, additions and further details about the analyses will be described in the Statistical Analysis Plan (SAP). After finalization of the SAP and unblinding, any additional analyses or changes to analyses that may be required will be fully disclosed in the clinical trial report.

11.1 DATA COLLECTION METHODS

This study will use web-based, electronic case report forms (eCRFs) developed through a validated, Electronic Records / Electronic Signatures-compliant platform (US Title 21 CFR Part 11).

All site personnel who will be using this system will receive formal training, after which each person will be issued a unique user name and password. Only the person who owns the user name and password will enter the system using that user name and password. For data security reasons and to be in compliance with regulatory guidelines, user names and passwords are not transferable.

The Investigator is responsible for all data entered via the electronic data capture (EDC) system eCRFs and must confirm the accuracy of the data by electronically approving (signing) the eCRFs. This responsibility includes the timely completion and accuracy of the data entered into the eCRFs by their site personnel.

The study center will be visited as frequently as documented in the Study Monitoring Plan to review the eCRFs for completeness and accuracy. The CRA will highlight any omissions, apparent errors, and values requiring further clarification using computerized and manual procedures and ensure that appropriate site personnel address the discrepancies. When a discrepancy results in corrected eCRF data, the correction will be recorded in the eCRF audit trail. Data collection procedures will be discussed during EDC system training.

Data from eCRFs and other external data will be entered into a clinical database as specified in the data management plan. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database.

11.2 SAMPLE SIZE CALCULATIONS

The sample size was chosen to provide observational safety data only. No formal sample size calculations were made.

11.3 POPULATIONS FOR ANALYSIS

Safety: The Safety population will be composed of all enrolled patients who received the study medication.

Intent-to-Treat (ITT): The ITT population will include all enrolled patients.

Modified Intent-To-Treat (mITT): The mITT population will include all enrolled patients who met all inclusion/exclusion criteria.

11.4 STUDY ENDPOINT ANALYSES

11.4.1 Efficacy Analyses

Although this study is primarily an observational safety study, some efficacy endpoints will be evaluated at the TOC Visit (Study Day 7-14) including:

- Clinical Outcome: A Clinical Outcome Responder is defined as a patient with all of the following:
  1) Resolution of abnormal vaginal discharge, and
  2) Negative 10% KOH Whiff test; and
  3) Clue cells less than 20% of the total epithelial cells on microscopic examination of the vaginal wet mount using saline.
- Nugent Score - TOC Visit [Study Day 7-14] score of 0-3 will be considered normal; a score of 4 and above will be considered abnormal.
- Investigator's Clinical Assessment - TOC Visit [Study Day 7-14]: Investigator's opinion of the need for additional BV treatment (Yes or No).
- Patient's Continued Clinical Response - Study Day 21-30 only: Investigator's opinion of the continued clinical response to treatment (Yes or No)

The mITT population will be used for analyses of efficacy endpoints. The number and percentage of patients will be summarized for each endpoint.

Patients with any missing data at TOC due to treatment failure or early discontinuation will be imputed as a non-responder for clinical outcome.

11.4.2 Safety Analyses

The following safety endpoints will be evaluated:

- **Adverse events (AEs):** Includes treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), treatment-related AEs, and AEs leading to study discontinuation.
- **Vital signs:** Blood pressure, temperature and pulse.
- **Physical examinations.**
- **Pelvic Examinations:** External genitalia and vagina
- **Laboratory assessments:** Includes serum chemistry, hematology and urinalysis.

11.4.2.1 *Statistical Methods for Safety Analyses*

Safety evaluations will be based on the incidence, intensity, and type of AEs, and changes invital signs, and clinical safety laboratory results. Safety variables will be tabulated and presented for all patients in the Safety population.

Summarization will focus on incidence of any SAEs; treatment-emergent AEs by System Organ Class (SOC) and Preferred term; and discontinuation rates. Each patient will be counted only once for each of the incidence rates, regardless of the

number of occurrences (events) the patient experiences.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) for purposes of summarization.

Treatment-emergent AEs will be tabulated, where treatment-emergent is defined as any AE that occurs after administration of the study drug and through the final visit, any event that is considered study drug-related regardless of the start date of the event, or any event that is present at baseline but worsens in intensity or is subsequently considered study drug-related by the Investigator. Adverse events that are considered study drug-related will also be tabulated.

12. STUDY ADMINISTRATION

12.1 REGULATORY AND ETHICAL CONSIDERATIONS

12.1.1 Regulatory Authority Approval

This study will be conducted in accordance with Good Clinical Practice (GCP) requirements described in the current revision of International Conference on Harmonization of Technical Requirements of Pharmaceuticals for Human Use (ICH) Guidelines and all applicable regulations, including current United States Code of Federal Regulations (CFR), Title 21, Parts 50, 54, 56, and 312 and Title 45, Part 164. Compliance with these regulations and guidelines also constitutes compliance with the ethical principles described in the current revision of the Declaration of Helsinki. This study will also be carried out in accordance with local legal requirements.

12.1.2 Ethics Approval

It is the Investigator's responsibility to ensure that, prior to initiating the study, this protocol is reviewed and approved by the appropriate local IRB/IEC. A non-local IRB/IEC may be used if the site of the study is not under the auspices of an IRB/IEC.

The IRB/IEC must also review and approve the site's informed consent form (ICF), other written information provided to the subject and all advertisements that may be used for subject recruitment. The Investigator will provide the Sponsor or designee with copies of these documents and of dated IRB/IEC approval(s) prior to the start of the study.

If it is necessary to amend the protocol or the ICF during the study, the Investigator will be responsible for ensuring that the IRB/IEC reviews and approves these amended documents. An IRB/IEC approval of the amended protocol and/or ICF must be obtained before implementation of the amended procedures and before new subjects are consented to participate in the study using the amended version of the ICF. The Investigator will forward copies of the dated IRB/IEC approval of the amended protocol and/or ICF to the sponsor or designee as soon as available.

12.1.3 Subject Informed Consent

Before being admitted to the clinical study, all subjects must consent to participate. An ICF will be given to each subject, which will contain all US federally required elements, all ICH-required elements, and Health Insurance Portability and Accountability Act Authorization (HIPAA) information in language that is understandable to the subject. The consent should note that the Investigator is receiving compensation for the expenses of conducting the study.

The process of obtaining the informed consent will be in compliance with all federal regulations, ICH requirements, and local laws.

The Investigator or a designee will review the study and the consent form with each subject. The review will include the nature, scope, procedures, and possible consequences of the subject's participation in the study. The consent and review must be in a form understandable to the subject. The Investigator or designee and the subject must both sign and date the ICF after review and before the subject can participate in the study. The subject will receive a signed and dated form, and the original will be retained in the site's study files. The Investigator or designee must emphasize to the subject that study participation is entirely voluntary and that consent regarding study participation may be withdrawn at any time without penalty or loss of benefits to which the subject is otherwise entitled.

12.1.4 Investigator Reporting Requirements

In accordance with applicable regulatory requirements, the Investigator is solely and exclusively obligated to keep the IRB/IEC informed of progress on this study, and/or provide periodic safety updates at his/her site, and notify the IRB/IEC of study closure.

The Investigator will provide the sponsor or designee with copies of all correspondence with, or from, the IRB/IEC that relates to study approvals, updates, or changes. Furthermore, the Investigator will be responsible for obtaining all IRB/IEC renewals according to applicable regulations for the duration of the study and to provide copies of any and all approval extensions to Lupin Research Inc.

12.2 PROTOCOL AMENDMENTS

Changes to the protocol can only be made by an approved protocol amendment. Protocol amendments must be approved by the Sponsor and IRB/IEC prior to implementation.

12.3 DECLARATION OF THE END OF THE CLINICAL TRIAL

For clinical trial sites located in the EU, a declaration of the end of the clinical trial will be made according to the procedures outlined in Directive 2001/20/EC, Article 10(c) and, for those countries outside the EU, local regulations will be followed.

12.4 STUDY MONITORING

In accordance with applicable regulations, GCP, and the procedures of the Sponsor, or its designee, the Study Monitor will periodically contact the site, including conducting on-site visits. The extent, nature, and frequency of on-site visits will be based on study complexity, enrollment rate, and data quality at the site. Through frequent communications (e.g., letter, e-mail, and telephone), the Study Monitor will ensure that the investigation is conducted according to protocol and regulatory requirements.

During these contacts, the monitoring activities will include:

- Checking and assessing the progress of the study
- Reviewing study data collected to date for completeness and accuracy

- Conducting source document verification by reviewing each subject's CRF against source documents (e.g., medical records, ICF, laboratory results reports, raw data collection forms), and
- Identifying any issues and addressing resolutions.

These activities will be done in order to verify that the:

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

The Investigator will allow the Study Monitor direct access to all relevant documents, and allocate his/her time and the time of his/her staff to the Study Monitor to discuss findings and any relevant issues.

In addition to contacts during the study, the Study Monitor will contact the site prior to the start of the study to discuss the protocol and data collection procedures with site personnel.

12.5 QUALITY ASSURANCE

At its discretion, the Sponsor or its designee may conduct a quality assurance audit of this study. Auditing procedures of the Sponsor and/or its designee will be followed in order to comply with GCP guidelines and ensure acceptability of the study data for registration purposes. If such an audit occurs, the Investigator will give the auditor direct access to all relevant documents, and will allocate his/her time and the time of his/her staff to the auditor as may be required to discuss findings and any relevant issues.

Regulatory agencies (e.g., FDA) may conduct an inspection of this study. In addition, EU clinical QP internal audit regulatory authorities may conduct an inspection for EU submission. If such an inspection occurs, the Investigator will allow the inspector direct access to all source documents, CRFs, and other study documentation for source data check and/or on-site audit inspection. The Investigator must allocate his/her time and the time of his/her staff to the inspector to discuss findings of any relevant issues.

12.6 STUDY TERMINATION AND SITE CLOSURE

Upon completion of the study, the following activities, when applicable, must be conducted by the Study Monitor in conjunction with the Investigator, as appropriate:

- Return of all study data to the Sponsor or its designee
- Data clarifications and/or resolutions
- Accounting, reconciliation, and final disposition of used and unused study drug
- Review of site study records for completeness; and

- Shipment of blood samples to the clinical laboratory.

Lupin Research Inc. reserves the right to temporarily suspend or prematurely terminate this study for any reason.

If the study is suspended or terminated for safety reason(s), Lupin Research Inc. will promptly inform the Investigator, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. The Investigator is responsible for promptly informing the IRB/IEC, and providing the reason(s) for the suspension or termination of the study.

If the study is prematurely discontinued, all study data must be returned to the Sponsor or its designee. In addition, the site must conduct final disposition of all unused study drug in accordance with Lupin Research Inc. procedures for the study.

12.7 SITE TERMINATION

Lupin Research Inc. may, in its sole discretion, terminate a single study site for various reasons, including, but not limited to, the following:

- Failure of the Investigator to enroll subjects into the study at a reasonable rate
- Failure of the Investigator to comply with pertinent FDA regulations
- Submission of knowingly false information from the research facility to the Sponsor, Study Monitor, or FDA
- Insufficient adherence to protocol requirements

If the participation of a study site is terminated for reasons other than safety (e.g., uncorrected data acquisition or image quality issues), Lupin Research Inc. will issue a written notice to the Investigator. The written notice will contain the reasons for taking such action. If a study site is terminated for noncompliance, Lupin Research Inc. will also notify appropriate regulatory authorities. Study termination and follow up will be performed in compliance with the conditions set forth in 21 CFR 312.50 and 21 CFR 312.56.

12.8 RECORDS RETENTION

In accordance with applicable regulatory requirements and following completion or termination of the study, the Investigator will retain a copy of all study records in a safe, secure, and accessible location for a minimum of 2 years after notification by Lupin Research Inc. that the investigations have been discontinued, or for 2 years after all marketing applications have been approved. For EU submissions, retention of a minimum 5 years though it was post-submission is required. Study records will include at a minimum the following:

- Signed ICFs for all subjects
- Subject identification list
- Record of all communications between the Investigator and the IRB/IEC

- Record of all communications between the Investigator and the Sponsor or its designee
- List of all sub-investigators and other key study personnel
- Copies of all financial records related to the study including: financial arrangements for the study; financial payments made by the Sponsor or its designee to the Investigator; and financial interests held by the Investigator in the product or in Lupin Research Inc.
- Copies of CRFs for all subjects, and
- All other source documents (e.g., subject records, hospital records, laboratory reports, and drug accountability records, etc.)

To avoid any possible errors, the Investigator will contact Lupin Research Inc. prior to the destruction of any study records. The Investigator must immediately notify Lupin Research Inc. in the event of accidental loss or destruction of any study records.

12.9 CONFIDENTIALITY OF INFORMATION

Subject names will remain confidential and will not be supplied to the Sponsor or its designee. Only the subject number, subject initials, and birth date will be recorded in the CRF. If the subject name appears on any other document collected (e.g., hospital discharge summary), it must be obliterated from the document before the document is transmitted to the Sponsor or its designee. All study findings will be stored in electronic databases. The subjects will give explicit written permission for representatives of the Sponsor, regulatory authorities, and the IRB/IEC to inspect their medical records to verify the information collected. Subjects will be informed that all personal information made available for inspection will be handled in the strictest confidence and in accordance with all state, local, and federal data protection/privacy laws, including, without limitation, the HIPAA.

When subjects complete the study, all contact information will be purged from all study files, and all subject identifiers (other than an assigned subject number) will be obliterated from documentation confirming a clinical endpoint event.

12.10 PAYMENT TO SUBJECTS

Subjects may be compensated for participating in this study and the amount of payment will be stated in the ICF approved by the IRB/IEC. Subjects not completing this study for whatever reason will be paid on a *pro rata* basis.

12.11 CLINICAL TRIAL REGISTRATION

This clinical trial will be registered on the "clinicaltrials.gov" clinical trial registry website as required by 42 USC 282(j).

13. REFERENCES

Koumans E.H., Sternberg M, Bruce C, et al. (2007) "The Prevalence of Bacterial Vaginosis in the United States, 2001-2004: Associations with Symptoms, Sexual Behaviors, and Reproductive Health." Sex Transm Dis. 34(11): 864-869

https://www.cdc.gov/std/bv/stdfact-bacterial-vaginosis.htm

Payne et al. (2010). "Evidence of African-American Women's Frustrations with Chronic, Recurrent Bacterial Vaginosis." Jn AANP 22(2010) 101-108.

IMS Health, 2014.

Hillier, S.L., et al. (2017). "Secnidazole Treatment of Bacterial Vaginosis: A Randomized Controlled Trial." Obstetrics & Gynecology 130(2): http://journals.lww.com/greenjournal/Abstract/publishahead/Secnidazole_Treatment_of_Bacterial_Vaginosis__A.98347.aspx.

Schwebke, J.R., et al. (2017). "A Phase 3, Double-blind, Placebo-controlled Study of the Effectiveness and Safety of Single Oral Doses of Secnidazole 2 g for the Treatment of Women with Bacterial Vaginosis." Retrieved from: http://www.ajog.org/article/S0002-9378(17)30964-X/fulltext.

Solosec [Package Insert]. Newark, NJ: Symbiomix Therapeutics, LLC.

14. APPENDIX A - SOLOSEC: PACKAGE INSERT AND LABEL INFORMATION