CLINICAL STUDY PROTOCOL

Protocol No. SEC-WH-301

A Phase 3, Multi-center, Prospective, Randomized, Placebo-Controlled, Delayed Treatment, Double-Blind Study to Evaluate the Effectiveness and Safety of a Single Oral Dose of Solosec® Granules Containing 2 grams of Secnidazole for the Treatment of Trichomoniasis

Protocol Version (Date):	**8 Feb 2019**
Amendment # 1 (Date):	**29 Mar 2019**
Sponsor:	**Lupin Inc.** **111 S Calvert St., Suite 2150** **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: 1. April. 2019

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INVESTIGATOR AGREEMENT

A Phase 3, Multi-center, Prospective, Randomized, Placebo-Controlled, Delayed Treatment, Double-Blind Study to Evaluate the Effectiveness and Safety of a Single Oral Dose of Solosec® Granules Containing 2 grams of Secnidazole for the Treatment of Trichomoniasis

Protocol Number: SEC-WH-301

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	

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1. SYNOPSIS

Protocol Number	SEC-WH-301
Title of Study	A Phase 3, Multi-center, Prospective, Randomized, Placebo-Controlled, Delayed Treatment, Double-Blind Study to Evaluate the Effectiveness and Safety of a Single Oral Dose of Solosec® Granules Containing 2 grams of Secnidazole for the Treatment of Trichomoniasis
Name of Active Ingredient(s)	secnidazole
IND/EudraCT No.	IND 117811
Indication	Solosec for the treatment of Trichomoniasis
Phase of Development	Phase 3
Investigational Center(s)	Approximately 10 study centers in the United States.
Objectives Primary Objective	The objective of this study is to evaluate the efficacy and safety of a single, oral dose of Solosec containing 2 grams of secnidazole compared to placebo for the treatment of trichomoniasis.
Secondary Objective	None
Study Design Overview	This is a Phase 3, multi-center, prospective, randomized, placebo-controlled, delayed treatment, double-blind, study to evaluate the effectiveness, and safety of a single, oral dose of Solosec containing 2 grams of secnidazole in female patients with trichomoniasis. Approximately 144 patients who test positive for trichomonas on OSOM® rapid test or via wet mount assessment or have positive *T. vaginalis* NAAT test within 30 days of screening (and have not been treated) and fulfill other eligibility criteria at the baseline visit will be enrolled in this study. The diagnosis of *T. vaginalis* will be confirmed by a positive culture for *T. vaginalis*. The study will consist of a primary study phase (Visit 1 (baseline) to Visit 2 (Day 6-12)) and a follow-up phase (Visit 2 to Visit 3 (7-12 days post Visit 2)). During the primary phase patients will be randomly assigned in a 1:1 ratio to either Solosec or placebo. The randomization will be stratified by site and based on the clinical symptoms of trichomoniasis (present or absent). Patients will return to the clinic for the "test of cure" (TOC) visit to be conducted on Days 6-12 (Visit 2). After all Visit 2 (V2) study procedures have been completed, patients will receive the opposite treatment (placebo patients will receive Solosec and vice versa). Patients with V2 cultures that are subsequently positive for *T. vaginalis* will return to the clinic for Visit 3 (V3) assessments and investigator assessment of need for additional therapy (an additional Visit 4 may be scheduled at the investigator's discretion if culture at V3 is positive). Patients with cultures that are negative at V2 will be contacted by phone and discharged from the study (no V3 required). A Schedule of Assessments is provided in Table 1.
Number of Patients Planned	Approximately 144 patients will be enrolled in order to obtain 100 patients (50 patients in each group) who will be included in the mITT study population (ie, culture-positive for trichomonas at baseline).

Diagnosis and Main Criteria for Enrollment	**Inclusion Criteria** Patients will be eligible to participate in the study if they meet all of the following criteria: 1. Are adult females or post-menarchal adolescent girls ≥ 12 years of age. 2. Are willing and able to give written informed consent or, if < 18 years of age, 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. Are 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/transdermal hormonal contraception, intrauterine device (IUD), barrier methods), tubal ligation or have a vasectomized partner or are practicing abstinence. 6. Have a diagnosis of trichomoniasis at the screening visit as determined by one of the following: • positive T. vaginalis NAAT test within 30 days of screening for which treatment has not been initiated. • positive OSOM® rapid test. • positive wet mount assessment. 7. Agree to abstain from vaginal intercourse until the final study visit. 8. Agree not to have any vaginal penetration or use of any vaginal products for the duration of the study (e.g., spermicides, condoms, diaphragms, vibrators, tampons, etc.). 9. Agree not to use vaginal douches, lubricants, or similar products for the duration of the study.
Exclusion Criteria	**Exclusion Criteria** Patients will be excluded from study participation if they have any of the following criteria: 1. Are pregnant, lactating, or planning to become pregnant during the study. 2. Are suspected clinically (or confirmed diagnostically) of having alternative causes of vaginal symptoms including symptomatic vulvovaginal candidiasis, chlamydia, gonorrhea, or an active genital herpes outbreak (Note: Chlamydia trachomatis, Neisseria gonorrhoeae [by PCR] results will not be available at time of randomization). Note: patients with bacterial vaginosis (BV) are eligible for this study. 3. Are suspected clinically of having an acute urinary tract infection. 4. Have active genital lesions, including primary syphilitic chancres and herpes simplex virus 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 may be enrolled). 5. Have received systemic antibacterial therapy or topical antimicrobial/antifungal/ immunomodulatory therapies in the genital area (vagina, vulva and surrounding soft tissue), within 14 days prior to the Baseline Visit (Day 1). 6. Have received secnidazole, metronidazole or tinidazole treatment within 30 days prior to the Baseline Visit (Day 1) or any other medication for the treatment of trichomoniasis within 30 days prior to Baseline Visit. 7. Are using NuvaRing® or any other vaginal ring products. 8. Have a history of drug or alcohol abuse within the past 12 months, as determined by the Investigator.

	9. Have participated in any investigational trial within 30 days before the Baseline Visit (Day 1). 10. Are participating in any investigational, observational or non-interventional study (either currently or during the study). 11. Have a known allergy to nitroimidazoles (e.g., metronidazole, tinidazole, nimorazole, secnidazole, etc.). 12. Inability to consume apple sauce or comply with study medication dosing instructions. 13. Have any history of cervical carcinoma or other carcinomas of the vagina or vulva or an abnormal Pap smear that may require colposcopic evaluation within the 3 months following the baseline visit (in the opinion of the investigator). 14. Have undiagnosed abnormal vaginal bleeding. 15. Are planning to undergo a surgical or vaginal procedure during the study. 16. Have any condition that interferes with their ability to understand or comply with the requirements of the study.
Study Endpoints Efficacy Endpoints	The following primary endpoint will be evaluated at the TOC Visit (Study Day 6-12): Microbiological Cure at the TOC Visit (Microbiological Cure is defined as a negative *T. vaginalis* culture).
Safety Endpoints	Includes treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), treatment-related AEs, and AEs leading to study discontinuation.
Exploratory Endpoints	Symptom resolution and microbiologic cure in the subgroup of patients who have baseline symptoms attributable to trichomoniasis.
Product, Dose, and Mode of Administration	Solosec (secnidazole) oral granules, 2g. Study medication will be orally administered, under direct observation, as a single dose with approximately 4 ounces of unsweetened applesauce. The study medication may be taken without regard to meals.
Placebo Product, Dose, and Mode of Administration	Matching placebo. Oral administration.
Statistical Methods Sample Size Determination	Assuming a responder rate (microbiological cure) of 75% in the Solosec treatment group and a 40% placebo response rate and based on the use of a two-sided, two-sample comparison of proportions at the alpha=0.05 level of significance, a sample size of 100 patients (50 patients in each group) who meet the mITT criteria will provide approximately 95% power to demonstrate a statistically significant difference between Solosec and placebo. Assuming 70% of patients randomized in the study will meet the mITT criteria, approximately 144 patients will be enrolled into the study.
Analysis of Primary Endpoint	**Study Populations**: **Intent-to-Treat (ITT):** The ITT population will include all randomized patients. **Modified Intent-To-Treat (mITT):** The mITT population will include all randomized patients who were culture positive for Trichomonas vaginalis and negative for other sexually transmitted infections. The primary efficacy analysis will be conducted in the mITT population. **Per-Protocol (PP):** The PP population will be composed of patients in the mITT population with consideration of the following criteria: received the study medication as randomized, met inclusion and exclusion criteria, had a TOC visit between Days 6-12, and had no major protocol violations. The composition of the PP population will be finalized and documented in a review of the data conducted prior to unblinding the study database. The PP population will be used for supportive efficacy analyses.

	Safety: The Safety population will be composed of all randomized patients who received any amount of study medication. The primary efficacy endpoint, Microbiological Cure (i.e., InPouch™ TV test negative for *T. vaginalis*) at the TOC visit, will be compared between the active and placebo treatment groups using a two-sided Cochran-Mantel-Haesnzel (CMH) test (stratified by the presence/absence of clinical symptoms of trichomoniasis at baseline) at the alpha=0.05 level of significance.

Table 1 Schedule of Assessments

Assessment	**Screening/ Baseline Visit**	**Visit 2** Test of Cure (TOC)	**Visit 3/4[6]** (only for Patients culture + at Visit 2)[8]
	Day 1/Visit 1	Day 6 -12	7-12 days post Visit 2 visit
Informed consent	X		
Inclusion/exclusion	X		
Demographics	X		
Medical history	X		
Vital signs	X	X	X
Height/weight	X		
Urine pregnancy test	X[1]	X[1]	X[1]
Physical examination	X	X[7]	X[7]
Pelvic examination	X	X	X
Clinical assessment of trichomoniasis symptoms (e.g., itching, discharge, odor)	X	X	X
OSOM® Trichomonas Rapid Test[2]	X		
Vaginal wet mount	X		X[5]
KOH Whiff Test	X		
pH of vaginal fluid	X		
T. vaginalis culture (BioMed InPouch™ TV test)	X[3]	X[3]	X[3]
STI Assessments	X		
IWRS Randomization	X		
Drug dosing	X	X[4]	
Concomitant medication review	X	X	X
Adverse events query	X	X	X
Investigator's clinical assessment of the need for further treatment			X

1. Performed by site personnel (not sent to central laboratory).
2. OSOM® test not needed if patient has positive NAAT test within 30 days of screening for which treatment has not been initiated. The manufacturer of OSOM® Trichomonas Rapid Test, Sekisui Diagnostics, does not recommend the test be used as a test of cure.
3. Results will not be available at the time of visit.
4. Patients who received placebo at first visit will receive Solosec and those who received Solosec at first visit will receive placebo.
5. For assessment of trichomonas only.
6. At the discretion of the investigator a patient who is culture positive at visit 3 may return for an additional visit (Visit 4) for further evaluation and treatment (assessments may include all those listed but at the discretion of the investigator).
7. A targeted physical examination is only needed per the Investigator's discretion if a reported AE requires further evaluation.
8. Patients with cultures that are negative at V2 or V3 will be contacted by phone and discharged from the study. Note: The telephone contact will include an assessment of safety and well-being. Subjects reporting any complaints, or an adverse event will be asked to return for an unscheduled visit for evaluation and safety assessment.

2. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine transaminase
API	Active pharmaceutical ingredient
AST	Aspartate transaminase
BID	Twice daily
BMI	Body mass index
BP	Blood pressure
BV	Bacterial vaginosis
CFR	Code of Federal Regulations
CMH	Cochran-Mantel-Haenszel
CO_2	Carbon dioxide
CRA	Clinical research associate
eCRF	Electronic Case Report Form
CRO	Clinical Research Organization
EDC	Electronic Data Capture
EOS	End of Study Visit
FDA	Food and Drug Administration
G	Gram
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HDPE	High-density polyethylene
HEENT	Head, eyes, ears, nose, and throat
HPV	Human papillomavirus
HSV-1	Herpes simplex virus Type 1
HSV-2	Herpes simplex virus Type 2
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intent-to-Treat

Abbreviation	Definition
IUD	Intrauterine Device
IWRS	Interactive Web Response System
Kg	Kilograms
KOH	Potassium Hydroxide
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
mITT	Modified Intent-to-Treat
mm Hg	Millimeter of mercury
NCE	New chemical entity
NF	National Formulary
OTC	Over-the-counter
PCR	polymerase chain reaction
PID	Pelvic inflammatory disease
PK	Pharmacokinetic
PO	Oral
RBC	Red blood cell count
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	System Organ Class
STI(s)	Sexually transmitted infection(s)
TMA	Transcription-mediated amplification
TOC	Test of Cure
US	United States
USP	United States Pharmacopeia
WBC	White blood cell count

3. INTRODUCTION

3.1 TRICHOMONIASIS

Trichomoniasis is a sexually transmitted disease caused by the parasite, *Trichomonas vaginalis* (*T. vaginalis,* TV). It is the most prevalent non-viral sexually transmitted infection in the United States, affecting an estimated 3.7 million persons (Satterwhite 2013). Health disparities persist in the epidemiology of *T. vaginalis* infection in the United States: TV infection prevalence was 4.2% among black males, 8.9% among black females, and 0.03% and 0.8%, respectively, among males and females of other races/ethnicities (Patel 2018). *T. vaginalis* infection affects >11% of women aged ≥40 years (Ginocchio 2012), and particularly high prevalence has been detected among STD clinic patients (Meites 2013) (26% of symptomatic women and 6.5% asymptomatic women tested) and incarcerated persons (9%–32% of incarcerated women [Sutcliffe 2010; Sosman 2011] and 2%–9% of incarcerated men) (Shuter 1998; Sosman 2005).

Some infected men have symptoms of urethritis, epididymitis, or prostatitis, and some infected women have vaginal discharge that might be diffuse, malodorous, or yellow-green with or without vulvar irritation. However, most infected persons (70%–85%) have minimal or no symptoms, and untreated infections might last for months to years (Peterman 2006; Sutton 2007). Although partners might be unaware of their infection, it is readily passed between sex partners during penile-vaginal sex (Sena 2007). Among persons who are sexually active, the best way to prevent trichomoniasis is through consistent and correct use of condoms during all penile-vaginal sexual encounters (Crosby 2012). Partners of men who have been circumcised might have a somewhat reduced risk of *T. vaginalis* infection (Sobngwi-Tambekou 2009; Gray 2009). Douching is not recommended because it might increase the risk for vaginal infections, including trichomoniasis (Tsai 2009).

T. vaginalis infection is associated with two- to threefold increased risk for HIV acquisition (McClelland 2007; Van Der Pol 2008), preterm birth, and other adverse pregnancy outcomes among pregnant women. Among women with HIV infection, *T. vaginalis* infection is associated with increased risk for pelvic inflammatory disease (PID) (Minkoff 1984; Cotch 1997, Moodley 2002).

Diagnostic testing for *T. vaginalis* should be performed in women seeking care for vaginal discharge. Screening might be considered for persons receiving care in high-prevalence settings (e.g., STD clinics and correctional facilities) and for asymptomatic persons at high risk for infection (e.g., persons with multiple sex partners, exchanging sex for payment, illicit drug use, or a history of STD). However, data are lacking on whether screening and treatment for asymptomatic trichomoniasis in high prevalence settings or persons at high risk can reduce any adverse health events and health disparities or reduce community burden of infection. Decisions about screening might be informed by local epidemiology of *T. vaginalis* infection (CDC Guidelines 2015).

3.1.1 Current Available Therapies

Current first-line therapeutic regimens recommended in the US by the Centers for Disease Control in their most recent Guideline, "Sexually Transmitted Diseases Treatment Guideline, 2015" (CDC 2015) for the treatment of trichomoniasis are as follows:

- Metronidazole 2 g in a single dose orally; or
- Tinidazole 2 g in a single dose orally; or
- Alternative regimen: Metronidazole 500 mg orally twice daily (BID) for 7 days;

3.2 INVESTIGATIONAL PRODUCT AND BACKGROUND INFORMATION

3.2.1 Solosec

Solosec® (secnidazole, SYM-1219) oral granules 2 g 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.

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 2 g (See the Solosec Package Insert, Appendix A for more detailed information). The efficacy of Solosec 2 g to treat patients with BV was demonstrated in two adequate and well-controlled studies; results were robust and consistent across all analyses in the two studies. In both studies, a greater percentage of patients receiving a single oral administration of Solosec 2 g achieved clinical response compared to placebo, i.e., 67.7% and 17.7%, respectively in SYM-1219-201 and 53.3% and 19.3%, respectively in SYM-1219-301. The treatment effect was statistically significant, $p < 0.001$ (adjusted CMH test) when compared to placebo.

Across the clinical studies, Solosec has been well tolerated. The most extensive clinical safety experience has been with Solosec 2 g administered to women with BV (n=518). Overall, with rare exception, AEs were mild or moderate in severity; severe AEs (n=9), SAEs (n=4), and study discontinuations due to AE (n=3) were rare across the BV studies. The commonly reported AEs that represent adverse drug reactions of Solosec in patients with BV were nausea, headache, and dysgeusia. Vulvovaginal mycotic infection and vulvovaginal candidiasis were reported in the BV studies but not in the healthy volunteer studies. Review of these events indicate that almost all of these infections were mild or moderate, resolved with treatment, and occurred more commonly in women receiving Solosec 2 g compared to placebo indicating that they were consistent clinically with secondary vaginal yeast infections, a known risk in women receiving antimicrobial treatment. No adverse trends were detected in hematology, chemistry, or vital signs parameters (See the Solosec Package Insert, Appendix A for more detailed information).

3.3 STUDY RATIONALE

Trichomoniasis is the most prevalent nonviral sexually transmitted infection in the United States, affecting an estimated 3.7 million persons (Satterwhite 2013); Lupin is developing Solosec as an available treatment option to provide an alternative, effective, single dose therapy for women diagnosed with trichomoniasis that, in turn, should decrease the known serious sequelae that occur when this infection is left untreated or ineffectively treated.

Drugs of the 5-nitroimidazole family are the only known medications to be effective against trichomoniasis (CDC 2015). Metronidazole, tinidazole, and secnidazole are reported to have about approximately 90-95% success rate in curing *T. vaginalis* (Cudmore 2004, Forna 2003, Hager 1980, Manorama 1978, Sobel 2015) depending on study design. Members of the 5-nitroimidazole family vary in half-life, C_{max}, and side effects. Secnidazole has been widely used outside the U.S. for many years. CDC currently recommends metronidazole 2 g orally in a single dose or tinidazole 2 g orally in a single dose (CDC 2015); metronidazole 500 mg BID for 7 days is recommended as the alternative treatment regimen.

Since cure rates with Solosec are anticipated to be high, this trial was designed to avoid the possibility of unprotected sex resulting in reinfection which becomes more likely the longer the interval between treatment and TOC. Peterman et. al. found a reinfection rate of 16.5% among women initially diagnosed and treated for *T. vaginalis* at baseline (Peterman 2006). In light of these data on clearance and chance for re-infection, a window for the TOC visit to be 6-12 days was selected. Since it is possible that this timing will create false positive NAAT (TMA) results and since reinfection in this group of women at high risk for STD is of greater importance to assess the efficacy of Solosec, trichomonas culture was selected as the criterion for cure.

3.4 DOSE SELECTION

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.

Secnidazole has been available for many years in Europe and other countries outside of the US as a single, oral 2 g dose, used as either monotherapy or in combination with other drugs. The drug has been used and investigated as a single or multiple dose regimen for the treatment of amebiasis, giardiasis, trichomoniasis and BV; there is a plethora of published literature on the use of secnidazole (Gillis 1996, Bravo 1978, Machado 1988, Moraes 2012, Piato 1977, Roche 1977, Siboulet 1977, Videau 1978).

Data demonstrate that secnidazole is efficacious for the treatment of BV as well as other infections, including trichomoniasis. The efficacy profile of secnidazole coupled with the tolerable safety profile and convenience of the dosing regimen (i.e., 1 single oral dose) suggest that it is an attractive alternative to other drugs in this class. Clinical investigation of secnidazole in the US for the treatment of trichomoniasis is warranted.

4. STUDY OBJECTIVES

4.1 PRIMARY OBJECTIVE(S)

The objective of this study is to evaluate the efficacy and safety of a single, oral dose of Solosec containing 2 grams of secnidazole compared to placebo for the treatment of trichomoniasis.

4.2 SECONDARY OBJECTIVE(S)

None.

4.3 STUDY ENDPOINTS

4.3.1 Primary Efficacy Endpoints

The following primary endpoint will be evaluated at the TOC Visit (Study Day 6-12):

- Microbiological Cure at the TOC Visit **(**Microbiological Cure is defined as a negative *T. vaginalis* culture).

4.3.2 Exploratory Efficacy Endpoints

Symptom resolution and microbiologic cure in the subgroup of patients who have baseline symptoms attributable to trichomoniasis.

4.3.3 Safety Endpoints

Treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), treatment-related AEs, and AEs leading to study discontinuation.

5. STUDY DESIGN

5.1 OVERALL STUDY DESIGN

This is a Phase 3, multi-center, prospective, randomized, placebo-controlled, delayed treatment, double-blind, study to evaluate the effectiveness, and safety of a single, oral dose of Solosec containing 2 grams of secnidazole in female patients with trichomoniasis. Approximately 144 patients who test positive for trichomonas on OSOM® rapid test or via wet mount assessment or have positive *T. vaginalis* NAAT test within 30 days of screening (and have not been treated) and fulfill other eligibility criteria at the baseline visit will be enrolled in this study. The diagnosis of *T. vaginalis* will be confirmed by a positive culture for *T. vaginalis*. The study will consist of a primary study phase (Visit 1 (baseline) to Visit 2 (Day 6-12)) and a follow-up phase (Visit 2 to Visit 3 (7-12 days post Visit 2)). During the primary phase patients will be randomly assigned in a 1:1 ratio to either Solosec or placebo. The randomization will be stratified by site and based on the clinical symptoms of trichomoniasis (present or absent). Patients will return to the clinic for the "test of cure" (TOC) visit to be conducted on Days 6-12 (Visit 2). After all Visit 2 (V2) study procedures have been completed, patients will receive the opposite treatment (placebo patients will receive Solosec and vice versa). Patients with V2 cultures that are subsequently positive for *T. vaginalis* will return to the clinic for Visit 3 (V3) assessments and investigator assessment of need for additional therapy (an additional Visit 4 may be scheduled at the investigator's discretion if culture at V3 is positive). Patients with cultures that are negative at V2 will be contacted by phone and discharged from the study (no V3 required). A Schedule of Assessments is provided in Table 1.

5.2 DOSE RATIONALE

Solosec (secnidazole) 2 g 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 144 patients will be enrolled by approximately 10 investigative sites in the United States in order to obtain 100 patients (50 patients in each group) who will be included in the mITT study population (i.e., culture-positive for *T. vaginalis* at baseline).

6.1 INCLUSION CRITERIA

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

1. Are adult females or post-menarchal adolescent girls ≥ 12 years of age.
2. Are willing and able to give written informed consent or, if < 18 years of age, 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. Are 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/transdermal hormonal contraception, intrauterine device (IUD), barrier methods), tubal ligation or have a vasectomized partner or are practicing abstinence.
6. Have a diagnosis of trichomoniasis at the screening visit as determined by one of the following:
   - positive *T. vaginalis* NAAT test within 30 days of screening for which treatment has not been initiated.
   - positive OSOM® rapid test.
   - positive wet mount assessment.

   Diagnosis will be confirmed by a positive culture for *T. vaginalis* obtained at the baseline visit (Note: The culture results will not be available at the time of study randomization and treatment).
7. Agree to abstain from vaginal intercourse until the final study visit.
8. Agree not to have any vaginal penetration or use of any vaginal products for the duration of the study (e.g., spermicides, condoms, diaphragms, vibrators, tampons, etc.).
9. Agree not to use vaginal douches, lubricants, 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 suspected clinically (or confirmed diagnostically) of having alternative causes of vaginal symptoms including symptomatic vulvovaginal candidiasis, chlamydia, gonorrhea, or an active genital herpes outbreak (Note: *Chlamydia trachomatis*, *Neisseria gonorrhoeae* [by PCR] results will not be available at time of randomization). Note: patients with bacterial vaginosis (BV) are eligible for this study.
3. Are suspected clinically of having an acute urinary tract infection.
4. Have active genital lesions, including primary syphilitic chancres and herpes simplex virus 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 may be enrolled).
5. Have received systemic antibacterial therapy or topical antimicrobial/antifungal/ immunomodulatory therapies in the genital area (vagina, vulva and surrounding soft tissue), within 14 days prior to the Baseline Visit (Day 1).
6. Have received secnidazole, metronidazole or tinidazole treatment within 30 days prior to the Baseline Visit (Day 1) or any other medication for the treatment of Trichomoniasis within 30 days prior to Baseline Visit.
7. Are using NuvaRing® or any other vaginal ring products.
8. Have a history of drug or alcohol abuse within the past 12 months, as determined by the Investigator.
9. Have participated in any investigational trial within 30 days before the Baseline Visit (Day 1).
10. Are participating in any investigational, observational or non-interventional study (either currently or during the study).
11. Have a known allergy to nitroimidazoles (e.g., metronidazole, tinidazole, nimorazole, secnidazole, etc.).
12. Inability to consume apple sauce or comply with study medication dosing instructions.
13. Have any history of cervical carcinoma or other carcinomas of the vagina or vulva or an abnormal Pap smear that may require colposcopic evaluation within the 3 months following the baseline visit (in the opinion of the investigator).
14. Have undiagnosed abnormal vaginal bleeding.
15. Are planning to undergo a surgical or vaginal procedure during the study.
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 double-blind 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:

- Physician decision
- 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
- Pregnancy
- Withdrawal by subject
- Study terminated by sponsor
- Protocol violation
- Disallowed concomitant medication. 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.
- Lost to follow-up. The Investigator will try to reach the patient, at least 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 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 their medical care.

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

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

7.1 TREATMENTS ADMINISTERED

Study medication [either Solosec (containing 2 grams of secnidazole) or matching placebo] will be orally administered, under direct observation, as a single dose with approximately 4 ounces of unsweetened applesauce. Upon completion of the primary phase (Visit 1 (baseline) to Visit 2 (Day 6-12)), patients will receive the opposite treatment (placebo patients will receive Solosec and vice versa).

The study medication may be taken without regard to meals. Water may be taken after the administration of study medication to aid in swallowing (See the Solosec Package Insert, Appendix A for more detailed information). Administration of each dose of study drug will be witnessed by a qualified study site staff member and documented on the source document.

All qualifying patients with *T. vaginalis* positive results at baseline will be asked to tell their sex partners (within at least 90 days) of their infection with *T. vaginalis* and to encourage them to seek appropriate treatment. Additionally, where allowed (based on legal and institutional restrictions) and at the discretion of the Investigator, all qualifying patients with *T. vaginalis* will be provided with a prescription for a medication for *T. vaginalis* (e.g., metronidazole 2g or tinidazole 2g) to deliver to their sex partner(s) (i.e., patient-delivered partner therapy).

7.2 IDENTITY OF INVESTIGATIONAL PRODUCT

The Solosec active formulation contains active secnidazole and excipients of sugar spheres, NF; povidone, USP; polyethylene glycol 4000, NF; Eudragit® NE30D (ethyl acrylate, methyl acrylate copolymer); talc, USP; and colloidal silicon dioxide, NF. The matching placebo contains the same ingredients as the active formulation with the exception of Solosec. Both the Solosec and placebo oral granules will be packaged in white packets with blinded packaging and labeling so they are indistinguishable.

Study drug labels will be prepared in accordance with applicable Federal Regulations and will not bear any statement that is false or misleading in any manner or represents that the study drug is safe or effective for the purposes for which it is being investigated.

Study medication must be stored at room temperature (20°- 25° C [68°- 77° F]); excursions permitted 15°C to 30°C (59°F to 86°F) [See USP Controlled Room temperature] (See the Solosec Package Insert, Appendix A for more detailed information).

7.3 SUPPLY OF STUDY MEDICATION

All study medication supplies will be provided by the sponsor.

7.4 METHOD OF ASSIGNING SUBJECTS TO TREATMENT GROUPS

The randomization will be stratified by site and based on the clinical symptoms of a trichomoniasis vaginal infection (present or absent).

Prior to the start of the study, a randomization list assigning kit numbers to one of two treatment groups in a 1:1 ratio will be generated by the CRO responsible for biostatistics in the trial. This list will be used by the manufacturer to package study drug into

treatment kits. Blinded study medication will be provided to the sites for each phase of the study (primary and follow-up phase). Study medication will be shipped to the study sites when IRB/IEC approval has been obtained and all required study documents are submitted to the sponsor.

Once it has been established that a patient is eligible to participate in this study, the eligible patient will be assigned a patient number in the EDC system, and a Visit 1 (primary phase) treatment kit from those kits that are available at the site will be assigned for that patient. The kit number for the follow-up phase treatment will be provided by IWRS at Visit 2. Treatment assignment must be assigned to patients using the IWRS.

7.5 BLINDING

This clinical trial is being conducted as a double-blind study; neither the investigator, supporting staff, nor the participant will be aware of the treatment the participant is receiving.

7.6 STUDY MEDICATION ACCOUNTABILITY

The US FDA requires accounting of all investigational drug received by each study center. Records of drug disposition required by federal law include the date received by the center, date administered, quantity administered, and the patient to whom study drug was administered. The Investigator is responsible for the accountability of all used and unused study drug containers and unused study drug.

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.

7.7 EMERGENCY CODE BREAKING

In case of a serious adverse event or pregnancy, the investigator may un-blind the subject's drug assignment when the study drug assignment is needed to make treatment decisions for the subject. The Sponsor should be notified of the event prior to breaking the code, if possible. If this is not possible, the Sponsor should be notified immediately afterwards, and the subject's drug code assignment should not be revealed to the Sponsor. The circumstances leading to the breaking of the code should be fully documented in the investigator's study files and in the subject's source documentation. The subject's treatment assignment should not be recorded in any study documents.

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;
- Secnidazole, metronidazole or tinidazole treatment.
- Intravaginal paromomycin, intravaginal boric acid, nitazoxanide, intravaginal betadine (povidone-iodine), clotrimazole, acetic acid, furazolidone, gentian violet, nonoxynol-9, and potassium permanganate.
- 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 final study visit.
- Patients should not have any vaginal penetration or use any vaginal products until after the study 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 at least two times during the study (Baseline Visit and TOC Visit on Days 6-12). An additional visit (V3) will be scheduled for all patients who are determined to be culture positive for *T. vaginalis* at Visit 2 per Table 1, Schedule of Assessments.

9.3 STUDY VISITS

9.3.1 Screening/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 prior and concomitant medication use;
5. Perform a urine pregnancy test;
6. Perform a physical exam, including vital signs, weight and height;
7. Perform a pelvic examination including assessment of vaginal discharge, and collection of vaginal samples as follows:
    a. Perform clinical assessment of trichomoniasis genital symptoms (e.g., itching, discharge, odor).
    b. Collect vaginal sample for *T. vaginalis* testing via:
        i. OSOM® Trichomonas Rapid test (If needed, see below).
        ii. BioMed InPouch™ TV test.
    c. Vaginal saline wet mount for assessment of clue cells and trichomonads;
    d. 10% KOH whiff test.
    e. pH of vaginal fluid;
    f. Collect samples for the assessment of other sexually transmitted infections (STIs) (*Neisseria gonorrhoeae*, *Chlamydia trachomatis*). Samples will be sent to central laboratory (results will not be available at time of enrollment);

8. Review inclusion and exclusion criteria. Note: Patients must have a diagnosis of trichomoniasis at the screening visit as determined by one of the following test results:
    i. Positive NAAT test within 30 days of screening for which treatment has not been initiated (NAAT test results must be available in the patient chart).
    ii. Positive wet mount assessment;
    iii. Positive OSOM® rapid test; note OSOM test not needed if patient has positive NAAT test within 30 days of screening for which treatment has not been initiated.

    Diagnosis will be confirmed by a positive culture for *T. vaginalis* obtained at the baseline visit.
9. If the patient meets all clinically available inclusion/exclusion criteria, the site will use the IWRS to randomize the patient into the study. IWRS will assign a unique kit number for the patient. The following procedures will be performed after the patient has been successfully randomized and Visit 1 Kit Number has been assigned:
    1. The patient will self-administer the study medication (without regard to meals). (See Section 7.1 for drug administration instructions)
    2. Schedule the TOC Visit for Study Day 6-12.

9.3.2 Visit 2/Test of Cure Visit (Study Day 6-12)

The Test of Cure (TOC) Visit should be conducted between Study Day 6 and 12.

The following procedures will be performed at the TOC 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 assessment of vaginal discharge, and collection of vaginal samples as follows:
    a. Perform clinical assessment of trichomoniasis genital symptoms (e.g., itching, discharge, odor).
    b. Collect vaginal sample for *T. vaginalis* testing via:
        i. BioMed InPouch™ TV test.

Upon completion of the primary phase (Visit 1 (baseline) to Visit 2 (Day 6-12)), the site will use IWRS to receive the Visit 2 kit number for the opposite treatment (placebo patients will receive Solosec and vice versa). Study treatment will be provided for the follow-up phase as described in section in Section 7 of the protocol.

The following procedures will be performed after the patient has been successfully completed the Day 6-12 TOC procedures described above:

1. The patient will self-administer the study medication (without regard to meals). (See Section 7.1 for drug administration instructions).

Patients with negative cultures for *T. vaginalis* at Visit 2 (i.e., negative InPouch™ TV test) will be contacted by phone and discharged from the study (no Visit 3 required). Note: The telephone contact will include an assessment of safety and well-being. Subjects reporting any complaints, or an adverse event will be asked to return for an unscheduled visit for evaluation and safety assessment.

A follow-up visit will be scheduled for all patients who have positive cultures for *T. vaginalis* (i.e., positive InPouch™ TV test at Visit 2).

Note: patients who are subsequently found to have a negative culture for T. vaginalis (i.e., negative InPouch™ TV test) from the sample obtained at the Baseline Visit (Day 1) should remain in the study and complete all appropriate study visits.

9.3.3 Visit 3 – Follow-up Visit (7-12 days post V2 visit)

A follow-up visit (V3) will be scheduled for all patients who have positive cultures for *T. vaginalis* (i.e., positive InPouch™ TV test) at Visit 2.

The following procedures will be performed at the Follow-up 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 assessment of vaginal discharge, and collection of vaginal samples as follows:
    a. Perform clinical assessment of trichomoniasis symptoms (e.g., itching, discharge, odor).
    b. Collect vaginal sample for *T. vaginalis* testing via:
        ii. BioMed's InPouch™ TV test.
        iii. Vaginal saline wet mount for assessment of trichomonads;
6. Investigator's assessment for the need of additional treatment.

Additional alternative treatment should be determined by the investigator based on his/her review of the vaginal wet mount assessment for active trichomonads. If clinical findings such as active trichomonads are not present on wet mount and the investigator does not believe patient should receive additional trichomoniasis treatment, then patient will be informed of findings and will await results of the Visit 3 InPouch TV test. Patients with negative cultures for *T. vaginalis* (i.e., negative InPouch™ TV test) at Visit 3 will be contacted by phone and discharged from the study (no Visit 4 required). Note: The telephone contact will include an assessment of safety and well-being. Subjects reporting

any complaints, or an adverse event will be asked to return for an unscheduled visit for evaluation and safety assessment. At the discretion of the investigator a patient who is culture positive at Visit 3 may return for an additional visit (V4) for further evaluation and treatment.

9.3.4 Unscheduled Visit

An unscheduled visit should be conducted for all patients with negative cultures for T. vaginalis at Visit 2 or Visit 3 (i.e., negative InPouch™ TV test) who report an adverse event during the post-visit telephone contact. Unscheduled visit procedures include further assessment of the reported AE and any additional follow-up procedure as listed in Section 9.3.3 above determined to be necessary by the study physician.

An unscheduled visit may be conducted in patients with positive STI results from the baseline visit in order to avoid unnecessary delays in treatment (See Section 9.4.8.4), in patients who are suspected of being pregnant (see Section 9.4.4), or at the discretion of the investigator.

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)

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 Visit (and at the follow-up visits, if needed).

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

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 Visit (Days 6-12) (and at the follow-up visits, if needed). 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 musculoskeletal, 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 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 vaginal discharge assessment and testing, will be performed at the Baseline Visit (Day 1) and TOC Visit (and at the follow-up visits, if needed). A non-lubricated speculum must be used during the pelvic examination. Components of the pelvic examination are specified in the following sections.

Prior to enrollment, if any test result is considered exclusionary it is not required to complete the evaluation of any additional samples.

9.4.7 Vaginal Discharge Assessment

During the pelvic examination, conduct clinical assessment of trichomoniasis symptoms (e.g., itching, discharge, odor) (record as Normal, or Abnormal consistent with TV, or Abnormal Other).

9.4.8 Vaginal Discharge Testing

Vaginal discharge testing will be performed at baseline and on each scheduled study day as indicated in the Schedule of Assessments, Table 1.

9.4.8.1 Trichomonas Vaginalis

OSOM® Trichomonas Rapid Test - Sekisui Diagnostics

The presence or absence of *T. vaginalis* will be determined by the Investigator, or designee using the OSOM® Trichomonas Rapid Test kit. 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).

The OSOM® Trichomonas Rapid Test will only be used at Visit 1 (baseline) to determine study eligibility. The OSOM test is not needed if patient qualifies for the study based on a positive NAAT test within 30 days of screening for which treatment has not been initiated.

Patients must have a diagnosis of trichomoniasis at the screening visit as determined by one of the following test results:

i. have positive NAAT test within 30 days of screening for which treatment has not been initiated (NAAT test results must be available in the patient chart).
ii. wet mount assessment;
iii. OSOM® rapid test; note OSOM test not needed if patient has positive NAAT test within 30 days of screening for which treatment has not been initiated.

InPouch™ TV (*Trichomonas vaginalis*) - BioMed Diagnostics, Inc.

The InPouch™ TV test will be utilized to determine the presence or absence of *Trichomonas vaginalis*. Commercial test kits will be provided to the sites, and vaginal samples will be obtained from the posterior fornix of the vagina by the Investigator, or trained designee according to the manufacturer's instructions. Specimens will be sent to a central laboratory. Detailed procedures for sample collection, analysis, and reporting will

be provided in a separate laboratory manual.

9.4.8.2 Wet Mount

Wet mount assessments will be performed at the Baseline Visit (Day 1). Additional, vaginal wet mount testing may be conducted at Visit 3 for further evaluation of trichomoniasis (See Table 1, Schedule of Assessments).

9.4.8.2.1 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:

9.4.8.2.2 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). Note: patients with bacterial vaginosis (BV) are eligible for this study.

9.4.8.2.3 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 and motile trichomonads,

- **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. Record clue cells as ≥ 20% of the total epithelial cells, or < 20% of the total epithelial cells.
- **Trichomonads:** Record motile trichomonads as Present or Absent.

9.4.8.3 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 < 4.7 or ≥ 4.7). The necessary materials and instructions will be provided for vaginal pH testing (refer to laboratory manual for instructions).

9.4.8.4 Sexually-transmitted Infection (STI) Assessments

Assessments for the presence of *Ne*isseria *gonorrhoeae* and *Chlamydia trachomatis* will be performed at the Baseline Visit (Day 1). Patients with positive STI results from the baseline visit should remain in the study and complete all specified procedures. An unscheduled visit may be conducted in order to avoid unnecessary delays in treatment.

Commercial test kits will be provided to the sites, and endocervical samples will be obtained by the Investigator, or trained designee according to the manufacturer's instructions. Specimens will be sent to a central laboratory. The necessary materials and instructions will be provided for STI testing (refer to laboratory manual for instructions).

9.5 INVESTIGATOR'S CLINICAL ASSESSMENT

At Visit 3 (if needed) the Investigator will answer the following question "In your opinion, does the patient require additional treatment for *T. vaginalis* 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 and followed-up outside of the study as they deem clinically necessary.

10. SAFETY AND PHARMACOVIGILANCE

10.1 DEFINITION OF AN ADVERSE EVENT

An AE is defined as any untoward medical occurrence in a clinical trial patient 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 medical condition or the worsening of a pre-existing condition will be considered an AE. Stable chronic medical conditions such as arthritis that are 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 patient.

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 drug administration will be considered to be "Non-Treatment-Emergent" AEs and those occurring after drug administration 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

The maximum severity for the event should be listed when the intensity changes during the course of an AE. If the change in severity represents distinct events rather than a single event, this should be recorded as separate AEs.

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 data are available to identify a clear alternative cause for the AE other than study drug; such as the patient's clinical state, concomitant therapy, and/or other interventions or the AE/SAE has no plausible temporal relationship to administration of study drug.

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 there is a plausible temporal relationship between the onset of the AE/SAE and study drug administration and the AE/SAE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the AE/SAE follows a known pattern of response to study drug; and/or the AE/SAE abates or resolves upon discontinuation of study drug or dose reduction and, if applicable, reappears upon re-challenge.

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.

10.4.1 Clinical Laboratory Abnormalities and Other Abnormal Assessments as AE:

Clinically significant abnormal laboratory findings or clinically significant abnormal findings from other assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs. Abnormal laboratory findings or other assessments deemed as abnormal will not be reported as AEs if they are determined to be clinically insignificant.

If an abnormal laboratory value or other assessment is clearly related to a medically-defined diagnosis or syndrome, the diagnosis or syndrome will be recorded on the AE form, not the individual laboratory values or assessment.

Clinically significant abnormal laboratory results or other clinically significant assessments will be followed until they resolve (return to normal or baseline values) or stabilize, or until they are judged by the Investigator to be no longer clinically significant.

Clinically significant abnormal laboratory findings or abnormal findings from other assessments that are present at baseline will be recorded as medical history.

10.4.1.1 Clinical Laboratory Abnormalities

It is the responsibility of the Investigator to assess the clinical significance of all abnormal laboratory values as defined by the appropriate reference range(s).

An abnormal laboratory value is considered to be an AE if the abnormality meets any of the following conditions below:

- results in discontinuation from the study
- requires treatment, modification/interruption of study drug dose, or any other therapeutic intervention
- is judged to be of significant clinical importance

Laboratory abnormalities that fulfill a seriousness criterion need to be documented as a SAE.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error, either by laboratory or by Investigator does not require reporting as an AE.

10.4.1.2 Other Safety Assessments:

Any abnormal finding determined from physical examinations or from other safety assessments (e.g., vital signs, ECGs, diagnostic imaging, or any other potential safety assessment required or not required by protocol) should be assessed for clinical significance by the Investigator. Only clinically significant abnormal findings should be recorded as an AE.

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.

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 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 Medical Monitor or designee as soon as possible after the investigator or site coordinator has become aware of its occurrence but no later than 24 hours of becoming aware of the event.

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. All completed SAE forms should be sent to sponsor's pharmacovigilance unit on the email: T301@lupin.com

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 Medical Monitor or designee.

The following information should be provided by the investigator or designee to accurately and completely record the event:

- Investigator name and center number
- Subject number
- Subject initials
- Subject demographics
- Clinical event
  - Description
  - Date of onset
  - Severity
  - Treatment (if blind needs to be broken)
  - Relationship to study drug (causality)
  - Action taken regarding study drug
- If the AE results in death
  - Cause of death (whether or not the death was related to study drug)
  - Autopsy findings (if available)
- Medical history case report form (copy)
- Concomitant medication case report form (copy)
- Any relevant reports (laboratory, discharge, x-ray, etc)

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.

The Medical Monitor for this study is:

Brajesh Pandey, MD
Title: Associate Medical Director, Lupin Inc.
Tel: 443-531-1109

Email: brajeshkumarpandey@lupin.com

Pregnancy reports: Pregnancy reports should be forward to the Sponsor pharmacovigilance unit for data-entry to the global safety database. This includes pregnancies without AE.

The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and presence or absence of any birth defect, congenital abnormalities or maternal and newborn complications.

The pregnancies reporting procedure should be the same as the SAE reporting procedure.

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 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

Assuming a responder rate (microbiological cure) of 75% in the Solosec treatment group and a 40% placebo response rate and based on the use of a two-sided, two-sample comparison of proportions at the alpha=0.05 level of significance, a sample size of 100 patients (50 patients in each group) who meet the mITT criteria will provide approximately 95% power to demonstrate a statistically significant difference between Solosec and placebo. Assuming 70% of patients randomized in the study will meet the mITT criteria, approximately 144 patients will be enrolled into the study.

11.3 POPULATIONS FOR ANALYSIS

Study Populations:

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

Modified Intent-To-Treat (mITT): The mITT population will include all randomized patients who were culture positive for Trichomonas vaginalis and negative for other sexually transmitted infections. The primary efficacy analysis will be conducted in the mITT population.

Per-Protocol (PP): The PP population will be composed of patients in the mITT population with consideration of the following criteria: received the study medication as randomized, met inclusion and exclusion criteria, had a TOC visit between Days 6-12, and had no major protocol violations. The composition of the PP population will be finalized and documented in a review of the data conducted prior to unblinding the study database. The PP population will be used for supportive efficacy analyses.

Safety: The Safety population will be composed of all randomized patients who received any amount of study medication. All safety summaries will be based on the Safety population.

11.4 INTERIM ANALYSES

There will be no interim analyses performed in this study.

11.5 STUDY ENDPOINT ANALYSES

11.5.1 Efficacy Analyses

Primary Efficacy Analysis

The primary efficacy endpoint, Microbiological Cure (i.e., InPouch™ TV test negative for *T. vaginalis*) at the TOC visit (Study Day 6-12), will be compared between the active and placebo treatment groups using a two-sided Cochran-Mantel-Haesnzel (CMH) test (stratified by the presence/absence of clinical symptoms of trichomoniasis at baseline) at the alpha=0.05 level of significance.

Exploratory Efficacy Analyses

The following exploratory endpoint will be evaluated at the TOC Visit (Study Day 6-12) for the subgroup of patients who have clinical symptoms of trichomoniasis at baseline:

- **Outcome Responder**: complete resolution of trichomoniasis symptoms (i.e., itching, discharge, and odor recorded as normal) and culture results (InPouch™ TV test) negative for *T. vaginalis*

11.5.2 Safety Analyses

Safety evaluations will be based on the incidence, intensity, and type of AEs. Safety variables will be tabulated and presented for all patients in the Safety population.

Summarization will focus on incidence of SAEs; treatment-emergent AEs by System Organ Class (SOC) and Preferred term; AEs that are considered study-drug related; and AEs leading to study discontinuation.

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

A Treatment-emergent AE 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.

11.6 GENERAL ISSUES FOR DATA ANALYSIS

11.6.1 Multiple Comparisons and Multiplicity

There is a single primary efficacy analysis, so no adjustment for multiplicity is required.

11.6.2 Covariates

The stratification variable of presence/absence of clinical symptoms of trichomoniasis at baseline will be included as a factor in the primary efficacy analysis.

11.6.3 Planned Sub-Group Analyses

The primary endpoint will be analyzed in each of the two randomization strata.

11.6.4 Missing Data

Subjects in the mITT population whose status for the primary endpoint is unknown will be assumed to be not cured. Apart from this, no imputation of missing data will be performed.

11.6.5 Pooling of Centers

Due to the small number of patients per center, all analyses and data summaries will be pooled across centers.

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. In addition, for those subjects who are 12-17 years old and are legally unable to sign an informed consent form, an IRB-approved assent form will be provided. 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 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 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 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 Inc. procedures for the study.

12.7 SITE TERMINATION

Lupin 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 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 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 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 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 Inc. prior to the destruction of any study records. The Investigator must immediately notify Lupin 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.

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

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APPENDIX A - SOLOSEC PACKAGE INSERT