Statistical Analysis Plan

Sponsor:	Lupin Inc.
Protocol No:	SEC-WH-301
Protocol Title:	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
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DOCUMENT HISTORY

Rev No	Date	Description
1.0	10-Apr-2019	Original document
2.0	20-Mar-2020	Added clarification that the presence/absence of clinical symptoms of trichomoniasis is based on symptoms reported during the baseline vaginal assessment, with a sensitivity analysis if this differs from the randomized strata.

TABLE OF CONTENTS

List of Abbreviations

AE	Adverse Event
BV	Bacterial Vaginosis
CMH	Cochran Mantel Haenszel
CRF	Case Report Form
EOS	End of Study
FDA	Food and Drug Administration
ITT	Intent to Treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent to Treat
NAAT	Nucleic Acid Amplification Testing
PP	Per-Protocol
SD	Standard Deviation
SOC	System Organ Class
TOC	Test of Cure
TV	*Trichomonas Vaginalis*
WHO	World Health Organization

1. INTRODUCTION

1.1 Study Background

Solosec® (secnidazole, SYM-1219) oral granules 2 grams is a Food and Drug Administration (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.

Trichomoniasis is the most prevalent nonviral sexually transmitted infection in the United States, affecting an estimated 3.7 million persons. 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.

1.2 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 *Trichomonas vaginalis* (*T. vaginalis,* TV) Nucleic Acid Amplification Testing (NAAT) 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).

1.3 Study Objectives

1.3.1 Primary Objectives

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.

1.3.2 Secondary Objectives

None.

2. STATISTICAL METHODOLOGY

2.1 General Principles

All analyses will be performed using SAS® software version 9.4. Prior and concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary Enhanced March 2019. Medical history and Adverse Events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 22.0.

Continuous variables will be summarized by n (number of patients with non-missing results), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized by count and percent (of patients in the population with a non-missing result).

All data collected will be presented in data listings. Data collected subsequent to TOC (Visits 3 and 4) will be included in data listings but will not be used for any analyses.

2.2 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.

2.3 Study Populations

Intent-to-Treat (ITT): The ITT population will include all randomized patients. Patients will be summarized based on the randomized treatment group.

Modified Intent-To-Treat (mITT): The mITT population will include all randomized patients who were culture positive for *T. vaginalis* and negative for STIs (lab results will not be known until after randomization). Patients will be summarized based on the randomized treatment group.

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.

Safety: The Safety population will be composed of all randomized patients who received any amount of study medication. Patients will be summarized based on the treatment group actually received.

2.4 Patient Accounting and Baseline Characteristics

Demographics will be summarized by treatment group for the mITT, PP, and safety populations. Other baseline characteristics (vaginal assessments, vital signs, laboratory results, medical history) and prior and concomitant medications will be summarized by treatment group for the safety population. Study completion status and primary reason for discontinuation will be displayed by treatment group for the ITT population.

2.5 Efficacy Analyses

The mITT population will be the primary efficacy population. The primary and exploratory efficacy analyses will also be conducted on the PP population. The presence/absence of clinical symptoms of trichomoniasis are based on symptoms reported during the baseline vaginal assessment.

2.5.1 Primary Efficacy Analyses

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. In the event that there are subjects whose actual symptom strata differs from the strata used for randomization, a sensitivity analysis will be conducted using the randomized strata to assess the impact of the strata differences.

2.5.2 Additional Analyses of Primary Endpoint

For each treatment group, an exact 95% binomial confidence interval of the cure rate will be calculated. Within each stratum, cure rates will be compared between the active and placebo treatment groups using a two-sided Fisher's exact test.

2.5.3 Exploratory Efficacy Analyses

The exploratory endpoint, Outcome Responder, will be evaluated at the TOC Visit (Study Day 6-12) for the subgroup of patients who have clinical symptoms of trichomoniasis at baseline. A patient is considered a responder if they have complete resolution of trichomoniasis symptoms (i.e., itching, discharge, and odor recorded as normal) and culture results (InPouch™ TV test) negative for *T. vaginalis*. Outcome Responders will be compared between the active and placebo treatment groups using a two-sided Fisher's exact test. For each treatment group, an exact 95% binomial confidence interval of the responder rate will be calculated.

2.6 Safety Analyses

Safety evaluations will be based on the incidence, intensity, and type of adverse events (AEs), and changes in vital signs. Safety summaries will be presented for all patients in the safety population.

2.6.1 Adverse Events

AEs that occur through the TOC Visit will be summarized by System Organ Class (SOC), Preferred Term, intensity, and treatment group for treatment-emergent AEs. Summaries will also be provided for study drug-related AEs, serious AEs, and AEs leading to study discontinuation. Each patient will be counted only once for each of the incidence rates, regardless of the number of occurrences (events) the patient experiences.

A Treatment-emergent AE is defined as any AE that occurs after administration of the study drug and through the final visit, or any event that is considered study drug-related regardless of the start date of the event.

2.6.2 Vital Signs

Actual values and changes from baseline to the TOC Visit will be summarized by treatment group for each vital sign assessment.

2.7 Interim Analyses

No interim analyses are planned.

3. DATA HANDLING

3.1 Baseline and Study Visits

Visits for all analyses will be as recorded on the Case Report Form (CRF). Baseline is defined as the last assessment (including unscheduled assessments) prior to dosing. The day of dosing is considered Day 1. Assessments will be considered Baseline if the assessment is before the date of dosing, or if the assessment was done on Day 1 and, according to the Study Schedule of Assessments, was supposed to be performed on Day 1 prior to treatment.

3.2 Missing Data

Patients in the mITT population whose status for the primary endpoint (Microbiological Cure) is unknown will be assumed to be not cured. Patients in the mITT subgroup of patients who have clinical symptoms of trichomoniasis at baseline whose status for the exploratory endpoint (Outcome Responder) is unknown will be assumed to be a non-responder. No other imputation of missing data will be performed.

3.3 Incomplete Medication Dates

If a medication has an incomplete start or stop date, the following rules will be used to determine if the medication is prior or concomitant:

- If the stop year and month are both present, the stop date will be assumed to be the minimum of the last day of the given month for the given year and the patient's final study date.
- If the stop year is present and the stop month is missing, the stop date will be assumed to be the minimum of the last day of the given year and the patient's final study date.
- Otherwise, if the stop year is missing, the stop date will be assumed to be the patient's final study date.

• An incomplete start date will be assumed to be the minimum of the date of study drug administration and the associated medication stop date.

4 CHANGES FROM THE PROTOCOL

This analysis plan clarifies that data subsequent to the TOC visit (Visits 3 and 4) will be included in data listings but will not be used in any analyses.

This analysis plan clarifies that the presence/absence of clinical symptoms of trichomoniasis is based on symptoms reported during the baseline vaginal assessment, with a sensitivity analysis if this differs from the randomized strata.