STUDY NO: FARMOVS 600/2004

PAREXEL NO: 71323

SPONSOR STUDY NO: IPM 004

A STUDY TO ASSESS THE PHARMACOKINETICS OF TMC120 VAGINAL MICROBICIDE GEL (TMC120 GEL-002) IN HEALTHY HIV-NEGATIVE WOMEN

SPONSOR:

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Dates:

Draft Version 1: 24 January 2005
Draft Version 2: 21 April 2005
Draft Version 3: 13 June 2005
Final Version: 22 June 2005
Revised according to Protocol Amendment No. 1: Final Version – 30 August 2005
Revised according to Protocol Amendment No. 2: Final Version - 09 January 2006

4.0 PROTOCOL SYNOPSIS

A STUDY TO ASSESS THE PHARMACOKINETICS OF TMC120 VAGINAL MICROBICIDE GEL (TMC120 GEL-002) IN HEALTHY HIV-NEGATIVE WOMEN

OBJECTIVES:	To assess plasma levels and pharmacokinetics of TMC120 applied vaginally. Doses of 2.5 mL of gel in concentrations of 0.001%, 0.005% and 0.02% will be applied for 10 consecutive days in healthy women. To measure vaginal tissue and vaginal fluid concentrations of TMC120 at various times after application of the gel. An exploratory analysis will assess whether urine levels of TMC120, or possible metabolites of TMC120, can be used to measure compliance with microbicide gel use for possible use in future large efficacy trials.
DESIGN:	Single-center, double-blind, randomized phase I study with volunteers randomized in a 1:1:1 ratio to receive 2.5 mL TMC120 Gel-002 at concentrations of 0.001%, 0.005% or 0.02% for 10 consecutive days.
STUDY POPULATION:	Healthy HIV-negative women ages $\geq$18 and $\leq$ 50 with no clinically detectable genital abnormality (including vulval, vaginal, cervical, and/or perineal pathology). Volunteers will be sexually abstinent for the duration of study product use.
SAMPLE SIZE:	18
TREATMENT REGIMEN:	Double blind randomization to receive TMC120 Gel-002 at concentrations of 0.001%, 0.005% or 0.02%, and self-application of 2.5 mL of study product with pre-filled applicators. On Days 1 and 10, study medication will only be applied in the morning. On Days 2 to 9, study medication will be applied twice daily, with the evening application approximately 12 hours after the morning application. The first gel application on Day 1will be applied by the volunteer at the site under the supervision of the investigator or registered nurse (direct observation is optional). Morning applications for each subject should be, as far as possible, on the same time each morning ($\pm$ one hour will be allowed). The time of administration of study product for each subject may vary to incorporate logistical procedures (e.g. availability of theatre for vaginal tissue biopsies). Treatment for urinary and genital infections (except HPV)

	will be provided. After randomization, a 7-day course of acyclovir will be provided for volunteers who developed HSV-2.
STUDY DURATION:	The anticipated study duration is approximately 3 months. Each volunteer's participation (from entry into the study) will be a maximum of 15 days.
CLINIC STAY:	Volunteers will stay in the clinic for 24 hours after the application of the study product on Days 1 and 10. They will be required to visit the clinic for the collection of additional blood samples.
BLOOD SAMPLES:	Blood samples for determination of plasma levels of TMC120 will be collected on the following times: • before application on Day 1 and at 30 minutes, 2, 4, 6, 8, 12 and 24 hours thereafter; • before application on Day 10 and at 2, 4, 6, 8, 12, 24, 36, 48, 72, 96, 108 and 120 hours thereafter.
VAGINAL WALL TISSUE SAMPLES:	Biopsies from the vaginal wall for determination of TMC120 concentrations in vaginal tissue will be taken at either 4, 12 or 24 hours after the application of the study product on Day 10. Volunteers will be randomized in a stratified block design within treatment groups in a 1:1:1 ratio to have biopsies of vaginal tissue taken at either 4, 12 or 24 hours (2 volunteers per concentration group at each time point).
VAGINAL FLUID SAMPLES:	Vaginal fluids will be collected via ~~Sno-Strips~~ ***Tear Flo Strips***™ at the following time-points: • before application on Day 1 and at 15 minutes, 1, 4 and 8 hours thereafter; • before application on Day 10 and prior to the cervicovaginal lavage and the vaginal tissue biopsy. Cervicovaginal lavage will be done on Day 10 prior to taking the vaginal tissue biopsy (after collection of vaginal fluid via ~~Sno-Strip~~ ***Tear Flo Strip***™).
URINE SAMPLES	Urine samples will be collected on Day 2 and Day 10.
SAFETY ASSESSMENTS:	Laboratory safety examinations (hematology, clinical chemistry, urine dipstick). Adverse events observation.
PHARMACOKINETIC VARIABLES:	The following pharmacokinetic variables will be calculated and presented (systemic compartment, on both Days 1 and 10):

	• Area under the plasma concentration-time curve (AUC) between administrations (total systemic exposure); • Clearance (Cl); • Apparent terminal half-life ($t_{½.z}$); • Volume of distribution (V_d). • Dose-linearity will be assessed. TMC120 concentrations in vaginal tissue and vaginal fluid will be measured at the specified time-points. TMC120 in urine will be measured at the specified time-points.
STATISTICAL ANALYSES:	Mean plasma levels per dose at Day 1 and 10 will be calculated, as well as the range and 95% confidence intervals at each time point. Mean concentrations for each dose, in vaginal tissue and vaginal fluid, will be calculated. Safety variables will be summarized by descriptive statistics.