

HPTN 076
Phase II Safety and Acceptability of an Investigational Injectable Product, TMC278 LA, for
Pre-Exposure Prophylaxis (PrEP)

A Study of the HIV Prevention Trials Network

Sponsored by:
Division of AIDS (DAIDS), United States (US) National Institute of Allergy and Infectious
Diseases (NIAID)
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IND Holder: PATH Drug Solutions (PDS)

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LIST OF ABBREVIATIONS AND ACRONYMS

AE	Adverse Event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine transaminase
aPTT	Activated partial thromboplastin time
ART	Antiretroviral therapy
ARV	Antiretroviral drug
AST	Aspartate transaminase
AUC	Area under the curve
βHCG	Beta human chorionic gonadotropin
CAB	Community Advisory Board
CBC	Complete blood count
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	Confidence intervals
CLIA	Continuous Laboratory Improvement Act of 1988
C _{max}	Maximum plasma concentration that a drug achieves after dosing
CMC	Clinical Management Committee
CPK	Creatine phosphokinase
CPQA	Clinical Pharmacology Quality Assurance
CRF	Case Report Form
CRM	Clinical Research Manager
CRPMC	(DAIDS) Clinical Research Products Management Center
CRS	Clinical Research Site
CT	<i>Chlamydia trachomatis</i>
CV	Coefficient of Variation
CYP	Cytochrome P450
DAERS	DAIDS Adverse Experience Reporting System
DAIDS	Division of AIDS
DAPY	Diaryl-pyrimidine
DMPA	Depo-Provera
DNA	Deoxyribonucleic Acid
DOT	Directly Observed Therapy
DSMB	Data and Safety Monitoring Board
EAE	Expedited Adverse Event
EC	Ethics Committee
EC ₅₀	Concentration of drug that gives half maximal effective response
eGFR	Estimated glomerular filtration rate
EFV	Efavirenz
EKG	Electrocardiogram
EQA	External Quality Assurance
ETR	Etravirine
F _{abs}	Absolute bioavailability
FDA	(United States) Food and Drug Administration
FGD	Focus Group Discussions
FSH	Follicle Stimulating Hormone
FTC/TDF	Emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF); Truvada®

GC	<i>Neisseria gonorrhoeae</i>
HIV	Human Immunodeficiency Virus
HPTN	HIV Prevention Trials Network
IB	Investigator Brochure
IATA	International Air Transport Association
IC ₅₀	Half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonization
IM	Intramuscular
IND	Investigational New Drug
INR	International normalized ratio
IoR	Investigator of Record
IQA	(DAIDS) Immunology Quality Assurance
IQR	Interquartile range
IRB	Institutional Review Board
IS	Injection site
ITT	Intention to treat
IUD	Intrauterine device
LC	(HPTN) Laboratory Center
LDMS	Laboratory Data Management System
LL	Local Laboratory
LOC	(HPTN) Leadership and Operations Center
LTFU	Loss-to-follow-up
MOP	(HPTN) Manual of Operations
MRC	(HPTN) Manuscript Review Committee
mRNA	Messenger RNA
MTN	Microbicide Trials Network
NIAID	(United States) National Institute of Allergy and Infectious Diseases
NIH	(United States) National Institutes of Health
NNRTI	Non-nucleoside reverse transcriptase inhibitor
ON	Options Now study
PD	Pharmacodynamic
PDS	PATH Drug Solutions
PEP	Post-Exposure prophylaxis
PI	Principal Investigator
PK	Pharmacokinetic
PR	the portion of the EKG between the onset of the P wave and the QRS complex
PrEP	Pre-exposure prophylaxis
PRO	(DAIDS) Protocol Registration Office
pSMILE	Patient Safety Monitoring in International Laboratories
PSRC	(DAIDS) Prevention Science Review Committee
PT	Prothrombin time
QA	Quality Assurance
QC	Quality Control
QD	Once daily dose
QRS	Interval from the beginning of the Q wave to the end of the S wave
QT	Time between the start of the Q wave and the end of the T wave
QTc	Corrected QT
QTcF	QT interval corrected with Fridericia's formula
RAM	Resistance associated mutations
RCT	Randomized clinical trial
RE	Regulatory Entity

RNA	Ribonucleic acid
RSC	Regulatory Support Center
RT	Reverse transcriptase
SAE	Serious Adverse Event
SDMC	(HPTN) Statistical and Data Management Center
SHIV	Simian HIV
SMC	Study Monitoring Committee
SOP	Standard Operating Procedures
SQ	Subcutaneous
SSA	Sub-Saharan Africa
SSP	Study Specific Procedures
STI	Sexually transmitted infection
SUSAR	Suspected unexpected serious adverse reaction
$T_{1/2}$	Apparent elimination half life
Tmax	Time to reach the maximum plasma concentration
TB	Tuberculosis
TDF	Tenofovir disoproxil fumarate
TdP	Torsade de Pointes
FTC/TDF	Emtricitabine/ tenofovir disoproxil fumarate (Truvada®)
TFV	Tenofovir
TMC278	Rilpivirine
TMC278 LA	Rilpivirine, Long Acting
UGT	UDP-glucuronosyl transferase
UL	Upper Limit of Normal
US	United States
USP	United States Pharmacopeia
VQA	(DAIDS) Virology Quality Assurance
WHO	World Health Organization
WT	Wild type

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PROTOCOL TEAM ROSTER

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IND Holder: PDS

I, the Investigator of Record (IoR), agree to conduct this study in full accordance with the provisions of this protocol. I will comply with all requirements regarding the obligations of investigators as outlined in the Statement of Investigator (Form FDA 1572), which I have also signed. I agree to maintain all study documentation for at least two years following the date of marketing approval for the study product for the indication in which it was studied, unless otherwise specified by DAIDS, or the HPTN Leadership and Operations Center (LOC). If no marketing application is filed, or if the application is not approved, the records will be retained for two years after the US Food and Drug Administration (FDA) is notified that the Investigational New Drug (IND) is discontinued. Publication of the results of this study will be governed by HPTN policies. Any presentation, abstract, or manuscript will be submitted to the HPTN Manuscript Review Committee (MRC), and DAIDS for review prior to submission.

I have read and understand the information in the Investigator's Brochure(s) (IB), including the potential risks and side effects of the products under investigation, and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

Name of Investigator of Record

Signature of Investigator of Record

Date

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SCHEMA

Purpose:	To evaluate the safety and acceptability of the injectable product, TMC278 LA, in healthy, human immunodeficiency virus (HIV)-uninfected women.
Design:	This is a multi-site, double-blinded, two-arm, two:one, randomized, trial comparing the safety of an intramuscular (IM) injection of TMC278 LA to a placebo given once every eight weeks over a 40 week period among sexually active, HIV-uninfected women. Approximately 132 women will be randomized.
Study Population:	HIV-uninfected women, ages 18-45.
Study Size:	The study will include approximately 132 women (defined as those receiving at least one injection) randomized as follows: 88 in the active product arm and 44 in the placebo arm.
Treatment Regimen:	Participants will be randomized to either the active product or the placebo arm. Participants randomized to active product will first be prescribed oral TMC278 (rilpivirine) 25 mg capsule, once daily for four weeks as an oral run-in and then will receive IM injections of active TMC278 LA, 1200 mg (formulation G001) at eight week intervals (Weeks 4, 12, 20, 28, 36 and 44). On each dosing occasion, 1200 mg of TMC278 LA will be delivered in two, 2 mL injections, one in each gluteus maximus muscle. Participants randomized to placebo will first be prescribed daily oral placebo for four weeks and then will receive saline (0.9% NaCl) in two, 2 mL injections, one in each gluteus maximus muscle at eight week intervals (Weeks 4, 12, 20, 28, 36 and 44).
Study Duration:	Total study duration is estimated to be approximately 100 weeks. Accrual will require approximately 24 weeks. Each subject will be enrolled and followed for a total of 76 weeks. Study participants will receive oral product for four weeks, then IM injections at eight week intervals (Weeks 4, 12, 20, 28, 36 and 44), and will be followed for 32 more weeks.

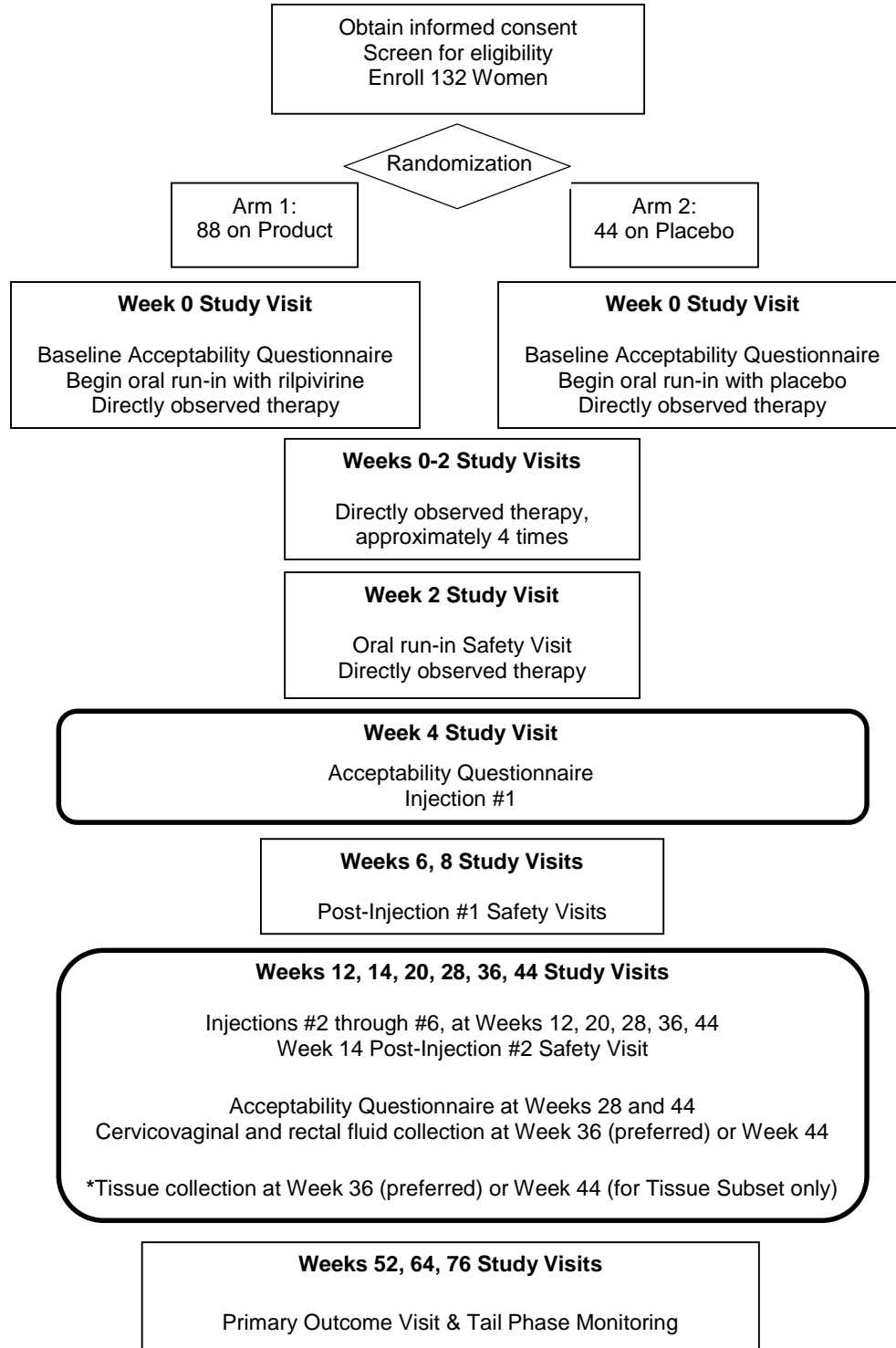
Primary Objective:	<ul style="list-style-type: none"> To evaluate the safety of the injectable product, TMC278 LA (1200 mg dose administered at Weeks 4, 12, 20, 28, 36 and 44), through 48 weeks after initial injection (at Week 52) in women in sub-Saharan Africa (SSA) and the US.
Primary Endpoint:	<ul style="list-style-type: none"> The primary safety endpoint is the proportion of participants in each arm experiencing any Grade 2 or higher clinical and laboratory AEs that occur from the initial injection to 8 weeks after the last injection (Week 52) among participants who receive at least one injection.
Secondary Objectives:	<ul style="list-style-type: none"> To evaluate the tolerability and acceptability of TMC278 LA. To describe the pharmacokinetics (PK) of TMC278 LA in plasma. To describe TMC278 LA concentration in cervicovaginal fluid and rectal fluid in participants, and in vaginal tissue in a subset of approximately 24 participants (US sites only). To evaluate the safety of rilpivirine (oral + injectable LA product) through Week 76 in women in SSA and the US. To estimate HIV incidence through study follow-up.
Secondary Endpoints:	<ul style="list-style-type: none"> The proportion of participants who would be interested in using the study product for HIV prevention in the future. The proportion of participants who do not receive the full regimen of study injections, in accordance with the protocol. Parent/metabolite concentration in plasma. Time to steady-state of TMC278 LA in plasma. Pre-dose (trough) concentrations at steady state in plasma. Apparent terminal elimination rate of TMC278 LA in plasma. Parent/metabolite concentration in cervicovaginal fluid, rectal fluid, and vaginal tissue. The proportion of women in each arm who experienced Grade 2 or higher clinical and laboratory AEs through Week 76. Number of participants acquiring HIV infections during study follow-up in each arm.
Exploratory Objective:	<ul style="list-style-type: none"> To genotype DNA from a subset of participants to assess genetic polymorphisms impacting antiretroviral drug (ARV) metabolism.

Study Sites:

- Bronx Prevention Center CRS, USA
- New Jersey Medical School CRS, USA
- Emavundleni CRS, Cape Town, South Africa
- Spilhaus CRS, Harare, Zimbabwe

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OVERVIEW OF STUDY DESIGN AND RANDOMIZATION SCHEME



*Vaginal tissue collection will be done at US sites in a subset of approximately 24 women at either Week 36 (preferred) or Week 44. Tissue collection will be done prior to any injections of TMC278 LA that occur during the same visit.

1.0 INTRODUCTION

1.1 Background and Prior Research

For thirty years the HIV epidemic has had a devastating public health impact, with almost 60 million men, women and children acquiring an HIV infection. In addition, nearly 25 million deaths have been attributed to the epidemic. More worrying still, in looking to the future, modeling exercises have indicated that staggering numbers of new infections may occur given current infection rates. The world may be facing 20 million to 60 million new HIV infections in the 15 to 20 years it may take to develop and evaluate a highly efficacious prophylactic vaccine.¹ Therefore finding effective alternative approaches to prevention in the shorter term² remains an urgency, particularly synergistic combinations of sociobehavioral and medical interventions.^{3,4} It is now envisaged that the HIV prevention “tool box” should include integrated strategies such as condom usage and male circumcision, as well as behavioral, biomedical and structural interventions for HIV-uninfected and HIV-infected individuals. Biomedical interventions currently under clinical development include both systemic and topical agents for PrEP for both men and women. The safety and efficacy of oral emtricitabine/ tenofovir disoproxil fumarate (FTC/TDF) in combination with other ARVs for antiretroviral therapy (ART), and results from FTC/TDF PrEP in a rhesus macaque rectal simian HIV (SHIV) exposure model, supported the development and evaluation of FTC/TDF for PrEP. Five randomized clinical trials (RCTs) have evaluated oral TDF or FTC/TDF as PrEP.⁵⁻⁹ See Table 1.

These randomized trials differ in several ways (as shown in Table 1), but in all adherence has been shown to be critically linked to effectiveness.^{10,11} Significantly, the FEM-PrEP and Microbicide Trials Network (MTN) 003 (VOICE) trials, both conducted in sexually active, young women in SSA and requiring adherence to a daily regimen, were either stopped for futility or showed no efficacy on completion and on further investigation, confirmed very poor adherence by trial participants to study product. Trials involving daily use of study product that have demonstrated efficacy in intention to treat (ITT) analyses⁵⁻⁷ have also shown a relationship between adherence to product and efficacy. The efficacy of a coitally-linked use of a vaginal microbicide gel [1% Tenofovir (TFV)] was demonstrated in CAPRISA 004. The “BAT24” regimen (administered up to 12 hours before and after sex) was devised as a way to assist women with adherence on the basis that sex is intermittent and that participants may find it easier to adhere to a regimen linked to coitus. The dosing strategy was developed taking into account women's needs primarily and was informed by the HIVNET 012 dosing strategy as well as other available data.

Table 1: Placebo-controlled efficacy trials of oral PrEP for HIV prevention²

Study (location)	Population	Design	Relative reduction in HIV incidence in intention-to-treat analysis	PrEP detection in blood samples from non-seroconverters	PrEP detection in blood samples from seroconverters	HIV protection estimate as related to high adherence	Ref
Completed trials (ordered by decreasing HIV risk reduction in primary intention-to-treat analysis)							
Partners PrEP Study (Kenya, Uganda)	4747 heterosexual men and women with known HIV infected partners (serodiscordant couples)	1:1:1 randomization to daily oral TDF, FTC/TDF, or placebo	TDF: 67% (95% CI 44-81%, p<0.0001) FTC/TDF: 75% (95% CI 55-87%, p<0.0001)	82%	31%	86% (TDF) 90% (FTC/TDF) in participants with detectable TFV levels	7
TDF2 Study (Botswana)	1219 heterosexual men and women	1:1 randomization to daily oral FTC/TDF or placebo	FTC/TDF: 63% (95% CI 22-83%, p=0.01)	79%	50%	78% excluding follow-up periods when subjects had no PrEP refills for >30 days	6
Bangkok Tenofovir Study (Thailand)	2413 injection drug users	1:1 randomization to daily oral TDF or placebo	TDF: 49% (95% CI 9.6-72.2%, p=0.01)	66%	39%	70% in case control analysis ²	2
iPrEx (Brazil, Ecuador, Peru, South Africa, Thailand, US)	2499 MSM and transgender women	1:1 randomization to daily oral FTC/TDF or placebo	FTC/TDF: 44% (95% CI 15-63%, p=0.005)	51%	9%	92% in subjects with detectable TFV levels	5

FEM-PrEP (Kenya, South Africa, Tanzania)	2120 women	1:1 randomization to daily oral FTC/TDF or placebo	FTC/TDF: 6% (p=0.8) No statistically significant reduction in HIV incidence	35-38% at a single visit, 26% at two consecutive visits	15-26%	Trial investigators assessed use of PrEP as too low to evaluate efficacy.	8
VOICE (South Africa, Uganda, Zimbabwe)	3019 women (plus 2010 women receiving TFV or placebo gel)	1:1:1 randomization to daily oral TDF, FTC/TDF, or placebo	TDF: -49% (p=0.07) FTC/TDF: -4% (p>0.2) No statistically significant reduction in HIV incidence	<30% of samples; ~50% of women never had TFV detected in any sample	Not yet available	Trial investigators assessed use of PrEP as too low to evaluate efficacy	12
Trials in progress							
IPERGAY (France, Canada)	1900 men who have sex with men	1:1 randomization to FTC/TDF or placebo, used “on demand”	FTC/TDF (intercourse-associated use): Results expected 2016.	Not yet available	Not yet available	Not yet available	

Oral FTC/TDF (Truvada®) was recently approved by the US FDA for PrEP to reduce the risk of sexually acquired HIV-1 in adults at high risk and the US Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) have offered interim guidance about its use.^{13,14} Although, the FTC/TDF combination provides an exciting new prevention tool, there are several reasons that alternative PrEP agents are needed, including: 1) side effect profiles may impact adherence; 2) FTC/TDF is occasionally associated with increased creatinine levels and decreased bone density; 3) although TFV has a relatively long half-life and penetrates genital tissues well, it does not concentrate in the cervix or vagina after a single dose, and this may reduce “forgiveness” in the protection of women if doses are missed;¹⁵ and 4) while emergence of resistance in break-through infection has been low in clinical trials to date, resistance remains a concern. Oral FTC/TDF is rapidly becoming the first line choice in combination ART for most countries, therefore cross-resistance to this drug will be detrimental. Alternative PrEP agents that have a higher threshold for resistance in which the emergence of resistance will not impact efficacy of first-line regimens, are urgently needed.

Since daily PrEP, in either oral or gel formulation, may be a difficult adherence goal for some healthy individuals, finding alternative dosing regimens is a priority. Therefore, development of alternative agents for PrEP, including long-acting injectable products, is an important undertaking. Such products have the potential to prevent HIV acquisition without relying on adherence to a daily oral or gel insertion regimen. Injectable products are widely used by women for contraception. In the future, an effective PrEP product has the potential to be combined with an effective contraceptive for prevention of both pregnancy and HIV infection, and would be a valuable tool for HIV prevention among women in SSA. This protocol describes a safety and acceptability investigation of a new formulation and a new route and dosing schedule of a previously US FDA-approved ARV. The injectable product that is being considered for PrEP in this protocol is the long-acting formulation of rilpivirine, TMC278 LA.

Men at-risk for HIV acquisition may also benefit from an injectable PrEP strategy and TMC278 LA should also be tested in men. Given recent developments in the field, women have been prioritized in this protocol.

1.2 TMC278 LA

1.2.1 Description

Rilpivirine (TMC278), a non-nucleoside reverse transcriptase inhibitor (NNRTI) is a substituted diaryl-pyrimidine (DAPY) derivative with potent antiviral activity against HIV. It is approved by the US FDA for once daily oral administration and is effective as part of treatment for ARV-naïve HIV-infected patients as rilpivirine 25 mg tablets. It is also co-formulated with TDF and FTC for use as a once-daily single fixed-dose combination (Complera™).

TMC278 LA is a novel poloxamer 338-containing formulation of TMC278. TMC278 LA is long-acting suspension and well-suited for delivery via IM injection and is currently being considered for both ART and HIV prevention. Detailed information about TMC278 and TMC278 LA can be found in the IB and is summarized below.¹⁶

1.2.2 Mechanism of Action

The mechanism of action of TMC278, an NNRTI, is similar to that of efavirenz (EFV) and has a half maximal inhibitory concentration (IC_{50}) of 0.42 nM in an in vitro reverse transcriptase (RT) enzyme inhibition assay.

1.3 In vitro Studies

TMC278 has demonstrated broad and robust antiretroviral activity against wild type (WT) HIV-1 group M isolates A, B, C, D, F, G, H, HIV-1/IIIB [sub-nanomolar concentration of drug that gives half maximal response (EC_{50})] and HIV-1 group O isolates (nanomolar EC_{50}). The TMC278 EC_{50} values observed in human monocyte-derived macrophages infected with HIV-1/Ba-L or HIV-1/ADA were comparable to those observed for HIV-1 group. TMC278 also had antiviral activity against HIV-2 and simian immunodeficiency virus, but no activity was observed against several non-HIV related viruses like the human hepatitis B virus, herpes simplex virus 2, human coronavirus, influenza A virus, and vaccinia virus. A selectivity index of approximately 8,000 indicated that TMC278 was a potent and specific inhibitor of HIV-1. A reduction in the antiviral activity of TMC278 was seen in the presence of 50% human serum and of 45 mg/mL human serum albumin, as demonstrated by median EC_{50} ratios of 18.5 and 39.2, respectively.¹⁶

TMC278 demonstrated antiviral activity on clinical isolates resistant to first generation NNRTIs. Cross-resistance between TMC278, and etravirine (ETR) as well as EFV was observed. However, K103N in isolation was not associated with resistance to TMC278. Rather, resistance to TMC278 was mostly driven by the combination of specific NNRTI resistance-associated mutations (RAMs) and not the total number of mutations. Resistance mutations emerging in HIV-1 isolates under selective pressure of TMC278 included combinations of V90I, L100I, K101E, V106A/I, V108I, E138G/K/Q/R, V179F/I, Y181C/I, V189I, G190E, H221Y, F227C, and M230I/L where E138R represented a newly-identified NNRTI RAM.¹⁶

1.4 Pre-clinical (Non-Human) Studies

1.4.1 Pharmacokinetics

The absolute bioavailability (F_{abs}) of oral TMC278 was 32%, 54%, 31%, and 24% in rats, rabbits, dogs, and cynomolgus monkeys, respectively. In general, maximum plasma concentrations (C_{max}) after single or multiple oral TMC278 administrations at lower dose levels were reached rapidly (< three hours). At higher dose levels, the plasma profiles showed a plateau until at least eight hours in all species. PK studies with different nanosuspension formulations of TMC278 LA in mice, rats, rabbits, dogs, and mini-pigs have confirmed the intended long-lasting systemic exposure to TMC278. In general, IM administration demonstrated more favorable plasma PK than subcutaneous (SQ) dosing. Studies in dogs with the poloxamer 338 (P338) formulations containing nanoparticles identified an optimal mean particle size of 200 nm for TMC278 LA. No gender differences in exposure (C_{max} and area under the curve (AUC) values) were seen after repeated IM administrations of TMC278 LA to mini-pigs or dogs.¹⁶

In vitro, TMC278 is highly protein bound (> 99%) in all animal species tested and in humans, with predominant affinity for albumin. TMC278 is widely distributed

throughout the body in animals. During tissue distribution studies in rats, highest concentrations were observed in adrenal glands, liver, brown fat, and kidney. In pregnant rats, orally administered ¹⁴C-TMC278 was distributed in the placenta and the fetus.¹⁶

1.4.2 Pharmacology

TMC278 demonstrated the potential to inhibit some potassium channels involved in cardiac action potential repolarization and to induce the time between the start of the Q wave and the end of the T wave (QT) interval prolongation in the rabbit ventricular wedge assay. However, studies in humans have concluded that prolongation was not associated with the 25 mg daily dose of TMC278.

1.4.3 Toxicology

Single and repeated oral dosing of TMC278 was safe in toxicology studies in mice (up to three months), rabbits (five days), rats (up to six months) and dogs (up to 12 months). TMC278 did not show a potential for genotoxicity, teratogenicity, phototoxicity, skin or eye membrane irritation, or delayed-type hypersensitization. TMC278 did not affect fertility, early embryonic development, pre- and postnatal development, or the immune system at oral doses ranging from 160 to 1600 mg/kg/day. The systemic effects of TMC278 were found to be reversible and the target organs were the adrenal cortex and the associated steroid biosynthesis, the reproductive organs, liver, kidney, thyroid, pituitary, the hematopoietic system and the coagulation system. Studies with TMC278 LA have not been associated with remarkable systemic effects in animals.¹⁶

Inflammatory reactions were noted with parenteral administration in mice, rats, pigs, rabbits, mini-pigs, and dogs that lessened over time and changed from acute to granulomatous reactions, the latter in association with granulocyte infiltration and small degree of necrosis. The effects after IM injection were more localized and slightly milder than those after SQ injection. In repeated dose studies with TMC278 LA, local effects comprising erythema and induration were noted. The local effects in terms of clinical symptoms and of histopathological lesions are considered to be a reaction to the deposited material rather than due to an irritating potential of TMC278 LA.¹⁶

1.4.4 Pharmacogenomic Analysis

The purpose of the pharmacogenomic analysis will be to determine whether genetic polymorphisms play a role in governing the variability among participants in the PK and pharmacodynamics (PD) of TMC278 LA when used for HIV PrEP. In particular, genotyping and measurement of the expression levels of drug-metabolizing enzymes (cytochromes P450 (CYP) and UDP-glucuronosyltransferases [UGT]) and drug transporters will be performed to provide information about potential genetic mechanisms that govern TMC278 LA exposure.

Preliminary studies performed at the HPTN Laboratory Center (LC) have revealed that polymorphic enzymes, including CYP3A5 and UGT1A4, play a major role in the biotransformation of TMC278. Prevalent variants of these enzymes result in a loss of activity, which could result in decreased ability of an individual to metabolize TMC278 LA, potentially leading to increased drug exposure and decreased drug clearance. This will be addressed in HPTN 076 as

an exploratory objective by genotyping DNA from a subset of study participants; DNA will be analyzed for the presence of polymorphisms in drug metabolizing genes and drug transporters, including CYP3A5 and UGT1A4 polymorphisms.

1.5 Metabolism

In humans, TMC278 is metabolized by both oxidative pathways and conjugation. No unique or major human metabolites have been identified. In vitro studies with human liver microsomes suggest a predominant role for CYP3A enzymes in the formation of the three most prominent (but still minor) metabolites in humans.¹⁶ Results of drug-drug interaction studies in healthy volunteers are consistent with the primary role of CYP3A isozymes.

1.6 Clinical Studies in Humans

1.6.1 Oral Formulation of TMC278

The safety, tolerability, PKs and efficacy of oral TMC278 is well established. As of 31 July 2012, 758 HIV-uninfected and 1052 HIV-infected participants have been dosed with oral TMC278 in clinical trials. More than 30 Phase I studies were completed in HIV-uninfected participants and one Phase I and two Phase IIa studies were completed in HIV-infected participants with oral TMC278. Efficacy and safety data are available from one Phase IIb study at Weeks 96 and 240 and from two Phase III studies at Weeks 48 and 96.¹⁶

For multiple dose studies with oral TMC278, 430 healthy subjects were included. Of these 30% were female. Overall 25% of 680 participants in Phase III were female.¹⁷⁻¹⁹

Pharmacokinetics

TMC278 exhibited linear PK parameters for concentration of drug that gives C_{max} and AUC after single and multiple oral dose administration up to a dose of 150 mg daily in healthy subjects. Steady-state concentrations are usually reached within 11 days of oral dosing. The half-life (mean $t_{1/2}$) after multiple dosing was approximately 45 hours. The mean C_{max} following administration of oral TMC278 25 mg once daily dose (QD) in healthy volunteers is 203.8 ng/mL and it increases in a dose proportional manner with increased doses (Study C103). Furthermore, there was no indication of changes in the PK parameters of TMC278 over a 96 week period (Study C204). A total of 22 drug-drug interaction studies have been completed to evaluate the PK interaction potential of TMC278 with certain ARVs and a variety of other drugs. The exposure to TMC278 can be affected by modulators of CYP3A4 enzyme activity and by drugs that decrease gastric acidity. Proton-pump inhibitors (e.g. omeprazole) should not be co-administered with oral TMC278 as this will decrease the exposure to TMC278 due to the increase in gastric pH. Histamine H2-receptor antagonists, however, can be used if administered either at least 12 hours before or at least four hours after intake of oral TMC278, and antacids can be used if administered either at least two hours before or at least four hours after intake of TMC278. Drugs that induce CYP3A4 activity (e.g. rifabutin and rifampin) can reduce the TMC278 exposure and should not be co-administered. Drugs that inhibit CYP3A4 activity (e.g. ketoconazole) can increase the exposure to TMC278,¹⁶ but no dose adjustment is necessary.

Safety and Tolerability Studies

The pooled safety data from 27 Phase I studies showed that oral TMC278 was generally safe and well tolerated when administered alone or co-administered with other drugs up to 150 mg daily. In Phase I studies of healthy volunteers, the most commonly reported adverse event (AE) was headache (27%). A total of 27.3% of participants in the multi-dose trials and 25% of participants in the single dose trials reported headache. There was one Grade 3 headache, assessed as doubtful related to TMC278. No headaches led to discontinuation. All other AEs were reported in less than ten percent of participants. AEs were mostly Grade 1 or 2 in severity. Two subjects (0.5%) treated with TMC278 in the multiple dose studies had a Grade 4 AE (increased lipase), one (0.3%) of which occurred during treatment with TMC278 alone, and led to discontinuation. Grade 3 and 4 AEs and AEs leading to discontinuation were reported in less than three percent of subjects. There was no relevant corrected QT (QTc) prolongation on TMC278 25 mg daily, the dose selected for Phase III and for marketing purposes, as confirmed by the study C152. Increases in QTc, which were dose-dependent, were observed in the study C131 at supratherapeutic doses of 75 and 300 mg daily. No deaths or Serious Adverse Events (SAEs) were reported in the Phase I studies.

In the Phase III trials, ECHO and THRIVE, TMC278 had a favorable safety profile compared to the control, EFV in treatment-naïve HIV-infected participants in combination with FTC/TDF, AZT/3TC, or ABC/3TC, for at least 96 weeks, and in extension beyond 96 weeks. The tolerability advantages (fewer discontinuations due to AEs including rash) of TMC278 at Week 48 were maintained at Week 96 in those trials. Specific monitoring of adrenal hormones, QT intervals corrected with Fridericia's formula (QTcF) by electrocardiograms (EKG) and estimated glomerular filtration rate (eGFR) did not result in any safety concerns. The most commonly reported AEs in the TMC278 group were headache (15.5%), nausea (14.6%), diarrhea (13.7%), nasopharyngitis (12.8%), insomnia (10.5%), and dizziness (10.2%), all with similar incidences in the control group, except for dizziness. Dizziness and rash were reported statistically significantly less on TMC278 than on the EFV control ($p < 0.0001$). The majority of AEs were Grade 1 or 2 in severity. The incidence of any Grade 3 or 4 AE was lower in the TMC278 group (17.5%) than in the control group (20.4%).

1.6.2 Parenteral Formulation of TMC278 LA

The PK, safety and tolerability of TMC278 LA were evaluated in three completed studies. To date, more than 150 individuals have been exposed to TMC278 LA in completed and ongoing studies.

In completed Phase I studies of TMC278 LA so far, there have been close to 70 female participants. The ongoing MWRI-01 study (see below) will add 60 participants, including a few male participants.²⁰

Overall, the injections have been well tolerated and safe. Injection site (IS) reactions have been the most common adverse events. There have been no safety or tolerability observations which preclude multiple dosing.

Study C146

In the Phase I study (C146) of the F004 formulation of TMC278 LA in 60 healthy volunteers, the safety and PK were evaluated for at least 12 weeks following a

single SQ or IM injection of a 200 mg, 400 mg, or 600 mg dose. The PK demonstrated dose proportionality and favorable safety and tolerability profiles. No serious Grade 3 and 4 AEs or rash were reported and injections were well tolerated. IM injections in the gluteus were well tolerated. This formulation, which had 100 mg/mL TMC278 and similar excipients to the current formulation, is no longer used in clinical development.

Study C158

In the Phase I C158 study, the safety, tolerability and PK of single doses (300 mg, n=6; 600 mg, n=6; and 1200 mg, n=5) of the current G001 formulation of TMC278 LA (300 ng/mL nanosuspension containing P338) were evaluated. PKs were followed up for at least 12 weeks after dosing, or until the individual TMC278 plasma concentration was below 20 ng/mL.

For all dose groups, after a single IM injection, there was an initially faster release of TMC278 over the first two-three days and a more gradual release thereafter. The median apparent time to reach maximum concentration (t_{\max}) was 11.5 days, 9.0 days, and 3.0 days after injection, for the 300, 600, and 1200 mg dose groups, respectively. The PK demonstrated dose proportionality. The mean C_{\max} following a single IM dose of TMC278 LA 1200 mg was 139.5 ng/mL. The plasma concentrations of TMC278, after single 300, 600, and 1200 mg IM doses of TMC278 LA, were well below the concentrations associated with QTc prolongation in humans (mean C_{\max} values of 636-1665 ng/mL).

Multi-dose administration was evaluated in the cohort of healthy individuals that received an initial dose of 1200 mg, followed by two doses of 600 mg at monthly (28 days) intervals. After each IM injection of 600 mg TMC278 LA, TMC278 plasma concentrations rapidly increased over the first days, with a median t_{\max} two to three days after IM injection. Thereafter, there was a more gradual release of TMC278 from the IS, resulting in a stable plasma concentration-time profile. No accumulation was observed between subsequent injections, implying that steady-state had likely been achieved after the loading dose of 1200 mg. The mean C_{\max} after the third injection (600 mg) was 132 ng/mL, the mean plasma concentration 28 days after this third injection was 64 ng/mL, and the mean $t_{1/2}$ was 91 days. During this study, no SAEs were reported, but Grade 1 rash and pain upon touch at the ISs were reported in one participant for each of the doses. In the multi-dose administration cohort, Grade 1 rash was also seen in one participant after the second injection, and the participant discontinued before the receiving the third injection. This event was subsequently diagnosed as a fungal skin infection rather than a drug-related rash. Vital signs, body temperature, and EKG profile were normal, with no effect on QTc intervals. Overall there were no AEs related to laboratory parameters. There were mild, transient and expected increases in some inflammatory parameters.

Study SSAT040

In the investigator-initiated SSAT040 study, also with the G001 LA formulation, 60 female and six male participants were enrolled and received a single dose of 1200 mg, 600 mg, or 300 mg of TMC278 LA and were followed for 84 days. This was a dose ranging adaptive design study. The objective of this study was to determine the PK of TMC278 LA in female genital tract and male rectal compartment. Of the females enrolled, greater than 50% were of African or Afro-Caribbean ancestry.

The results from this study showed reasonable penetration of the product into the genital tract,^{20,21} and limited issues with tolerance and safety. In the female participants who received the 1200 mg dose, the C_{max} was 160.2 ng/mL in plasma and 199.9 ng/mL in cervicovaginal fluid.

Full data from this study are not available yet. However, in May 2012 one HIV seroconversion was reported. The participant, a 32 year old female, had been exposed to and infected with HIV during the course of her study participation. (Retrospective analysis of plasma confirmed that she was HIV negative at entry to the study.) She received 300 mg TMC278 LA intramuscularly on 9 January 2012 and complied with the study restrictions on abstinence from intercourse during the first 28 days of trial participation. In February 2012, she met a new regular partner (who reported a HIV negative rapid-test in February 2012, but has since been newly diagnosed as HIV positive). While barrier prevention (condom) was used on most occasions during intercourse, in retrospect she recalls that compliance was not 100%. She reported a single event of unprotected vaginal exposure occurring on February 19, three days prior to the day 42 study visit at which rilpivirine concentration in cervicovaginal fluid was measured at 18.3 ng/mL and rilpivirine in plasma was 10.5 ng/mL. Notably, the PK values in this subject were in range of other subjects also receiving 300 mg TMC278 LA. Retrospectively, a detectable viral load was first recorded on March 6 (Day 56) and HIV antibodies were present on April 2 (Day 84).

This event suggests that a single IM dose of 300 mg TMC278 LA will fail to prevent HIV transmission in an unknown proportion of patients six weeks after administration, suggesting that a higher dose is advisable for this Phase II study.

Study TMC278-MWRI01 (Options Now [ON])

An ongoing Phase I study, TMC278-MWRI-01, is an open-label, multi-arm, adaptive dose-ranging study that compares several dosing regimens of TMC278 LA, is designed to investigate safety/tolerability and whether the agent can protect genital tract tissues against HIV infection in an explant model.²² There could be up to six cohorts in this study, with two arms receiving either a 600 mg or 1200 mg single dose. Following the analysis of the first two cohorts, additional doses or multiple dosing of a selected dose may be evaluated. In the rest of the arms, a dose will be selected to be administered every two or three months, or a loading dose will be followed by a reduced dose every two or three months as one of the multi-dose regimens.

1.7 Rationale for dosing

Preliminary data from studies mentioned inform the PK and safety of 300, 600, and 1200 mg doses. The highest dose of TMC278 LA for PrEP that would be considered for further development is 1200 mg. Extensive modeling work by Janssen pharmacometricians, based on prior clinical studies of rilpivirine and antiviral effect data from the treatment development program, indicates that an 8-week dosing interval will provide sustained antiviral concentration in plasma throughout the 2-month period. Therefore, the safety of multiple dosing of TMC278 LA (1200 mg dose administered every eight weeks) in HIV-uninfected women in SSA and the US will be evaluated in the proposed study. Particular attention will be given to monitoring rash and pain upon touch at the ISSs. In addition, cardiac electrical activity will be closely monitored with EKGs on all participants. All clinical and laboratory AEs as well as all SAEs will be

evaluated across arms. The acceptability of injections of a 2 mL volume into each gluteus maximus muscle every eight weeks also needs to be determined, since this is expected to be the highest feasible dose. The rationale for choosing an eight week dosing interval is the belief that women wanting PrEP would not find a four week interval between clinic visits acceptable. An eight week interval is more likely to fit with use of a depot contraceptive product such as Net-EN. The oral run-in phase is included to screen out, before the first injection, any individual who experiences a treatment-related AE such as a maculopapular rash or other treatment-related AEs, Grade 2 and higher. Since there is relatively little safety information in multiple dosing of this product, an oral run-in was thought to be salient in this phase 2 study. Participants will be observed while taking the study product by site staff on approximately six occasions during the first two weeks of the oral run-in:

- Week 0 Visit (Enrollment)
- Week 2 Visit (Oral Run-in Safety Visit), and
- four separate Directly Observed Therapy (DOT) visits (between Weeks 0 and 2).

It is hoped that with the accumulation of sufficient data, the oral run-in may be discontinued in further development of this product. To understand concentration-response relationships of TMC278 LA and its HIV preventive effect, knowledge of drug concentrations achieved in relevant anatomic compartments (blood plasma, vaginal tissue, cervicovaginal fluid, and rectal fluid), assessed in this protocol, is critical information needed for planning future studies. In addition, TMC278 metabolism is significant and complex. The proposed dose and schedule of dosing have not been studied in humans, apart from helpful and careful pharmacometric modeling. Further, the expression of the relevant metabolizing enzymes may vary across relevant anatomic sites, resulting in a variety of unexpected metabolites. While this is primarily a safety study, it provides an important opportunity to confirm the pharmacometric models of TMC278 concentrations over time, and to explore the metabolic variations in blood plasma, tissue, and luminal fluid relevant to TMC278 clearance. These data will be useful for more complex pharmacometric, multi-compartment modeling which may significantly inform clinical trial simulations and study design in the future.

2.0 STUDY OBJECTIVES AND DESIGN

2.1 Primary Objective

The primary objective of this study is as follows:

- To evaluate the safety of the injectable product, TMC278 LA (1200 mg dose administered at Weeks 4, 12, 20, 28, 36 and 44), through 48 weeks after initial injection (at Week 52) in women in SSA and the US.

2.2 Secondary Objectives

The secondary objectives of this study are as follow:

- To evaluate the tolerability and acceptability of TMC278 LA.
- To describe the PK of TMC278 LA in plasma.

- To describe TMC278 LA concentration in cervicovaginal fluid and rectal fluid in participants, and in vaginal tissue in a subset of approximately 24 participants (US sites only).
- To evaluate the safety of rilpivirine (oral + injectable LA product) through Week 76 in women in SSA and the US.
- To estimate HIV incidence through study follow-up.

2.3 Exploratory Objective

The exploratory objective of this study is as follows:

- To genotype DNA from a subset of participants to assess genetic polymorphisms impacting ARV metabolism.

2.4 Study Design

This is a multi-site, double-blinded, two-arm, two:one randomized, placebo-controlled trial comparing the safety of TMC278 LA for 48 weeks after the initial IM injection to a saline (0.9%NaCl) placebo IM injection among sexually active, HIV-uninfected women who are assessed by the clinic staff as being at “low risk” for HIV acquisition (in keeping with a safety trial). Approximately 132 women will be randomized to TMC278 LA and placebo in approximately a two:one ratio (88 and 44 in the TMC278 LA and placebo arm, respectively). Approximately 96 women will be enrolled in SSA and approximately 36 women will be enrolled in the US. In order to screen for initial safety and tolerability of the active product, a run-in period with oral rilpivirine will precede the injection of TMC278 LA. Participants randomized to the placebo arm will receive oral placebo capsules prior to injection of saline solution (0.9%NaCl). Participants will be observed while taking the study product by site staff on approximately six occasions during the first two weeks of the oral run-in at Week 0 (Enrollment), at Week 2 (Oral Run-in Safety Visit), and on four separate DOT visits between Weeks 0 and 2. Cervicovaginal and rectal fluid will be collected for PK studies at a single follow-up visit. A subset of approximately 24 women at US sites will have vaginal tissue collection for PK studies at a single follow-up visit (Tissue Subset).

Participants who present with Grade 2 or greater RELATED AEs during the oral-run in phase will not receive the injectable TMC278 LA. Participants who present with Grade 3 or 4 UNRELATED AEs will not proceed to the injectable phase unless approved by the Clinical Management Committee (CMC).

Arm 1: Participants randomized to the active arm will receive rilpivirine 25 mg capsules once daily for four weeks to be taken orally with a meal. Participants will then receive IM injections of TMC278 LA, 1200 mg dose, at eight week intervals (at Weeks 4, 12, 20, 28, 36 and 44). On each dosing occasion 1200 mg of TMC278 LA will be delivered in two, 2 mL injections, one in each gluteus maximus muscle. All participants will receive a total of six doses (12 IM injections).

Arm 2: Participants randomized to the placebo arm will receive placebo capsules once daily for four weeks to be taken orally with a meal. Participants will then receive IM

injections of saline (0.9% NaCl) at eight week intervals (at Weeks 4, 12, 20, 28, 36 and 44). On each dosing occasion placebo will be delivered in two, 2 mL injections, one in each gluteus maximus muscle. All participants will receive a total of six doses (12 IM injections).

2.5 Study Duration

Total study duration is estimated to be approximately 100 weeks. Accrual will require approximately 24 weeks. Each participant will be enrolled and followed for a total of 76 weeks. During the 76 weeks, study participants will receive oral product for four weeks, then injections at eight week intervals (Weeks 4, 12, 20, 28, 36 and 44), and will be followed for 32 more weeks.

3.0 STUDY POPULATION

The study population will consist of approximately 132 women (defined as those who receive at least one injection) between the ages of 18-45 years who are eligible based on the inclusion and exclusion criteria listed below.

Approximately 96 participants will be enrolled in SSA (64 and 32 in the TMC278 LA and placebo arms, respectively) and approximately 36 at the two combined US sites (24 and 12 in the TMC278 LA and placebo arms, respectively).

3.1 Inclusion Criteria

Women who meet all of the following criteria will be eligible for inclusion in the study:

- Women, 18 - 45 years (inclusive) of age at Enrollment
- Female at birth
- Willing and able to provide informed consent to take part in the study
- Willing and able to provide adequate locator information
- Willing and able to provide acceptability and adherence assessments throughout the study
- Understands and agrees to local reporting requirements for sexually transmitted infections (STIs)
- No evidence of an active STI, women who have an STI (*Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (GC), or syphilis) identified at the Screening visit are ineligible*
- Per participant report, no diagnosis of GC, CT, or syphilis in the last 6 months
- Availability to return for all study visits and participate in all study-related procedures, barring unforeseen circumstances
- Per participant report, using (or willing to use) an acceptable form of contraception (e.g., intrauterine device [IUD], hormonal contraception [DMPA], oral, injectable, transdermal patch, implants) from screening until one month after last study visit or surgical sterilization of the participant
- Must agree to use condoms for the duration of the study
- Must agree not to participate in other concurrent drug or vaccine trials
- Normal laboratory values**

- HIV tests performed at Screening and Enrollment are non-reactive/negative (see Study Specific Procedures (SSP) Manual)
- Hemoglobin (women) ≥ 10.5 g/dL
- Absolute neutrophil count $\geq 1,000$ cells/mm³
- Platelet count $\geq 100,000$ /mm³
- Calculated creatinine clearance ≥ 70 mL/minute using the Cockcroft-Gault equation
- Alanine aminotransferase (AST) and aspartate aminotransferase (ALT) < 2 times the upper limit of normal (ULN)
- Total bilirubin < 2.5 ULN
- Urine protein $< 2+$

*Women who have an STI identified at the Screening visit (CT, GC, or syphilis) will be provided treatment but are ineligible. Women who report having CT, GC, or syphilis in the last six months are ineligible.

** Specimens for Screening labs must be obtained within 28 days prior to study Enrollment.

3.1.1 Inclusion Criteria for the Tissue Subset (US sites only)

A subset of approximately 24 participants at US sites will participate in more intensive sampling of vaginal tissue during Week 36 (preferred) or Week 44.

For these participants, the following additional criteria need to be met:

- Satisfactory Pap results in the 12 calendar months prior to biopsy consistent with Grade 0 according to the Female Genital Grading Table for Use in Microbicide Studies Addendum 1 to the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009), or satisfactory evaluation with no treatment required of Grade 1 or higher Pap result per American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines in the 12 calendar months prior to biopsy is required, as indicated.

If there is no documentation of satisfactory Pap results, and if indicated, the participant should be offered to have the test performed by the site prior to enrollment in the Tissue Subset. If Pap testing is indicated and participants decline, they are not eligible for the Tissue Subset.

- In addition to documentation of satisfactory Pap results, women must have normal laboratory results for coagulation tests to be eligible for the Tissue Subset. Abnormal coagulation test results may indicate an increased risk of bleeding.
- Women have to be willing to abstain from vaginal intercourse and practices involving insertion of anything in the vagina (drug, douche, penis, or sex toy) for 3 days prior to vaginal biopsy and for 7 days post-biopsy, to minimize risk of HIV-1 infection and bleeding complications after the procedure.
- Participants must not be pregnant at the time of vaginal sampling, based on pregnancy test results from previous visits and on the result of urine pregnancy test performed on the same day before the proposed vaginal sampling.

- Women undergoing biopsy must have received all prior injections of study product, in accordance with the protocol, to be eligible for inclusion.

3.2 Exclusion Criteria

Women who meet any of the following criteria will be excluded from the study:

- Experiencing early menopause using clinical criteria (amenorrhea greater than six months in absence of pregnancy) or a prior report of an abnormal Follicle Stimulating Hormone (FSH) test
- PrEP or post-exposure prophylaxis (PEP) for HIV exposure within 90 days prior to Screening
- Pregnant or last pregnancy outcome 90 days or less prior to Screening
- Currently breastfeeding
- Intends to become pregnant during the period of study participation
- Experiencing uncontrolled depression or active suicidal ideation
- History of recurrent urticaria
- Any history of anaphylaxis or severe allergy resulting in angioedema
- Any serious acute, chronic, or progressive disease (e.g. known history of neoplasm, cancer, insulin-dependent diabetes, cardiac disease, auto-immune disease), or with signs of cardiac disease, renal failure, or severe malnutrition
- Any laboratory abnormalities that are Grade 2 or higher, according to the DAIDS Toxicology tables (excluding the lab values for AST, ALT, and bilirubin listed in the inclusion criteria) (please see Section 6.1 for a list of Screening laboratory tests)
- Recreational injection drug use in the 52 weeks prior to screening
- Participating or plans to participate in another research study involving study drugs, vaccines or medical devices
- Participated in another research study involving study drugs, vaccines or medical devices within the four weeks prior to screening; may be longer than four weeks depending on half-life of study drug
- Past participation in an HIV vaccine study
- Has plans to relocate and cannot attend the visits at the clinic
- Per participant report at Screening, current or anticipated ongoing use and/or unwillingness to abstain from contraindicated medications or supplements (listed in the SSP Manual)
- Abnormal resting EKG at screening including:
 - Abnormal sinus rhythm (heart rate below 40 or above 100 beats per minute)
 - QTcF interval > 450 ms
 - QRS interval < 50 ms
 - QRS interval > 120 ms
 - PR interval > 210 ms
- History of additional risk factors for Torsade de Pointes (TdP), such as heart failure, hypokalemia, hypomagnesemia, family history of known long QT syndrome, or sudden death at young age (≤ 40 years) in a first-degree relative (i.e., biological parent, sibling, or offspring)
- Currently active Tuberculosis (TB), or undergoing treatment for the same (by self-report)

- Any signs or symptoms consistent with acute (pre-seroconversion) HIV infection, or self-reported concern about recent HIV infection
- Any reactive or positive HIV test at Screening or Enrollment, even if the person is confirmed to be HIV-uninfected
- Has any other condition that, in the opinion of the site IoR or designee, would preclude informed consent, make study participation unsafe, interfere with adherence, complicate interpretation of study outcome data, or otherwise interfere with achieving study objectives (e.g., at increased risk of cardiovascular events)

Women who do not meet eligibility criteria because of an abnormal EKG, risk factors for TdP, an STI (GC, CT, or syphilis) present at Screening or report of an STI (GC, CT, or syphilis) in the past 6 months, or a history of arrhythmia may not be re-screened.

Women who present at Screening with symptoms consistent with an acute HIV infection or who have a reactive HIV test may not be re-screened. Women who do not meet eligibility criteria for the study for other reason(s) may be re-screened at a future date at the discretion of the site IoR.

3.2.1 Exclusion Criteria for the Tissue Subset (US sites only)

Participants of the Tissue Subset must meet the above eligibility criteria to be enrolled in HPTN 076. Participants interested in participating in the Tissue Subset must meet additional inclusion and exclusion criteria. Women who meet any of the following criteria will be excluded from the Tissue Subset:

- Unwillingness to abstain from the following medications for a period of 10 days before a biopsy procedure:
 - Aspirin*
 - Non-steroidal anti-inflammatory drugs (NSAIDS)

*Daily use of low-dose aspirin (no more than 81 mg) is allowed at the discretion of the IoR.
- Unwillingness to abstain from the following medications for 3 days prior to vaginal biopsy and for 7 days post-biopsy: Heparin, including Lovenox®, Warfarin, Plavix® (clopidogrel bisulfate), and any other drugs that are associated with increased risk of bleeding following biopsy procedures at the discretion of the IoR.
- Carcinoma in situ of the cervix or invasive cervical cancer. Abnormalities of the vaginal mucosa or significant vaginal symptom(s), which in the opinion of the IoR represent a contraindication to biopsy (including but not limited to presence of any unresolved injury, and infectious or inflammatory condition of the local mucosa).
- Hysterectomy.

3.3 Recruitment Process

Each Clinical Research Site (CRS) in SSA will be responsible for enrolling approximately 48 women from their communities. Each CRS in the US will be responsible for enrolling approximately 18 women from their communities.

3.4 Co-Enrollment Guidelines

Women participating in other studies involving HIV prevention, vaccines and/or devices will not be eligible for enrollment in HPTN 076. In addition, co-enrollment in any such studies during the HPTN 076 study will not be permitted and women must agree not to enroll in these types of studies during HPTN 076.

3.5 Participant Retention

Once a participant enrolls in this study, the study site will make every reasonable effort to retain her for 76 weeks of study activities to minimize possible bias associated with loss-to-follow-up (LTFU) (four weeks of oral run-in; 40 weeks of product injection; 32 weeks of follow-up). Study site staff members are responsible for developing and implementing local standard operating procedures (SOPs) to target this goal. Components of such procedures could include:

- Thorough explanation of the study visit schedule and procedural requirements during the informed consent process and re-emphasis at each study visit.
- Thorough explanation of the importance of both study treatment groups to the overall success of the study.
- Collection of detailed locator information at the Screening Visit, and active review and updating of this information at each subsequent visit.
- Use of appropriate and timely visit reminder mechanisms.
- Immediate and multifaceted follow-up on missed visits.
- Mobilization of trained outreach workers or “tracers” to complete in-person contact with participants at their homes and/or other community locations with participant permission.
- Regular communication with the study community at large to increase awareness about HIV/Acquired Immunodeficiency Syndrome (AIDS) and explain the purpose of HIV prevention research and the importance of completing research study visits.

3.6 Participant Withdrawal

Regardless of the participant retention methods just described, participants may voluntarily withdraw from the study for any reason at any time. The IoR may also withdraw participants from the study in order to protect their safety and/or if they are unwilling or unable to comply with required study procedures after consultation with the Protocol Chair, DAIDS Medical Officer, Statistical and Data Management Center (SDMC) Protocol Statistician, and LOC Clinical Research Manager (CRM).

Participants also may be withdrawn if the study sponsor, government or regulatory authorities, or site Institutional Review Boards (IRBs)/Ethics Committees (ECs) terminate the study prior to its planned end date.

Every reasonable effort will be made to complete a final evaluation of participants who terminate from the study prior to the Week 76 study visit, and study staff will record the reason(s) for all withdrawals from the study in participants' study records.

Participants who discontinue treatment shall be maintained in follow-up as originally scheduled whenever possible.

4.0 STUDY PRODUCT

4.1 Product Formulation/Content

This is a multi-site, double-blinded, two-arm, two:one randomized, placebo-controlled trial. Participants will be randomized prior to receiving any product, and that randomization will be maintained throughout the study. Participants will either be randomized to Arm 1 (active) or Arm 2 (placebo).

Study Capsules for Oral Run-in Phase

Arm 1 (Active Arm): Participants randomized to the active arm will receive rilpivirine 25 mg capsules daily for four weeks. Rilpivirine 25 mg capsules contain (27.5 mg) rilpivirine hydrochloride equivalent to 25 mg rilpivirine. Rilpivirine 25 mg capsules must be stored in the original bottle to protect them from light between 15-30°C (59°-86°F).

Arm 2 (Placebo Arm): Participants randomized to the placebo arm will receive placebo capsules daily for four weeks. Placebo for rilpivirine capsules must be stored in the original bottle to protect them from light between 15-30°C (59°-86°F).

Study Product for Injection Phase

After four weeks of oral run-in, participants will receive injections. Injections are given at six time points (Weeks 4, 12, 20, 28, 36 and 44).

Arm 1 (Active Arm): Participants randomized to the active arm will receive TMC278 LA. TMC278 LA is a novel poloxamer 338-containing formulation of TMC278, chemical name 4-[[4-[[4-[(E)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino] benzonitrile. TMC278 LA is a sterile, aqueous, nanosuspension formulation (G001) provided as a 300 mg/mL extended release suspension in 600 mg/2 mL per vials. TMC278 LA is for IM use only.

TMC278 LA is supplied in a carton containing two single use vials of TMC278 LA 600 mg/2 mL in each vial. TMC278 LA vials must be stored in the original container to protect them from light between 2-8°C (36°-46°F). Do not freeze. Further information on TMC278 LA is available in the current IB.

Arm 2 (Placebo Arm): Participants randomized to the placebo arm will receive placebo for TMC278 LA.

0.9% Sodium Chloride (NaCl) for Injection, United States Pharmacopeia (USP) in a single use vial will be used as the placebo for TMC278 LA and must be stored at 20°– 25°C (68°-77°F) [See USP controlled room temperature].”

4.2 Product Regimen(s) and Administration

Oral Run-in Phase

Arm 1 (Active Arm): Participants randomized to the active arm will take rilpivirine 25 mg capsule, one capsule orally once daily with a meal for four weeks starting at Week 0.

Arm 2 (Placebo Arm): Participants randomized to placebo arm will take placebo for rilpivirine capsule, one capsule orally once daily with a meal for four weeks starting at Week 0.

Injection Phase

Arm 1 (Active Arm): At the end of the four week oral run-in period, participants who were randomized to the active arm will begin TMC278 LA injections. Injections will be given at eight week intervals (Weeks 4, 12, 20, 28, 36 and 44).

TMC278 LA, 1200 mg/4 mL dose will be prepared by the pharmacist using aseptic technique and divided into two injections of 600 mg/2 mL in each syringe. The prepared syringe containing 600 mg/2 mL will be administered IM in the gluteus maximus muscle of each buttock.

The prepared TMC278 LA injectable dose in a syringe must be administered to the study participant within 2 hours of preparation.

Study product preparation details are included in the HPTN 076 SSP.

Arm 2 (Placebo Arm): At the end of the four week oral run-in period, participants who were randomized to the placebo arm will begin placebo for TMC278 LA injections. Injections will be given at eight week intervals (Weeks 4, 12, 20, 28, 36 and 44).

0.9% NaCl for Injection, USP will be used as placebo for TMC278 LA. The 0.9% NaCl for Injection, USP 4 mL dose will be prepared by the pharmacist using aseptic technique and divided into two injections of 2 mL in each syringe. The prepared syringe containing 2 mL of 0.9% NaCl for Injection, USP will be administered IM in the gluteus maximus muscle of each buttock.

The prepared placebo for TMC278 LA injectable dose in a syringe must be administered to the study participant within 2 hours of preparation.

Study product preparation details are included in the HPTN 076 SSP.

4.3 Product Supply and Accountability

Study Product Supply

Rilpivirine 25 mg capsule, placebo for rilpivirine capsule, and TMC278 LA 600 mg/2 mL extended release suspension in a vial are manufactured by Janssen R&D and provided by PDS.

0.9% NaCl for Injection, USP in a single use vial is provided by PDS.

Study Product Acquisition by the Site

Rilpivirine 25 mg capsule, placebo for rilpivirine capsule, TMC278 LA suspension for injection in a vial, and 0.9% NaCl for Injection in a vial will be supplied to the study sites

by the NIAID Clinical Research Products Management Center (CRPMC). The study site pharmacist may obtain rilpivirine and TMC278 LA through the CRPMC by following the instructions in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trial Networks*, and instructions in the SSP Manual.

Study Product Accountability

The site pharmacist must maintain complete records of all study products received from the NIAID CRPMC and subsequently dispensed to study participants. All unused study products must either be returned to the NIAID CRPMC or destroyed after the study is completed/terminated. At the end of the study, specific instructions will be provided for the return or destruction of the study products.

4.4 Adherence Assessment

Oral Run-in Phase

When the study product is dispensed on site, participants will be counseled about the importance of taking the pills on a daily basis with a meal.

Participants will be observed while taking the study product by site staff on approximately six occasions during the first two weeks of the oral run-in (at Week 0, at Week 2, and on four separate DOT visits between Weeks 0 and 2). Participants will also be given adherence counseling at DOT visits and at Week 2. Pill counts will be conducted during at least two of the DOT visits and at Week 2.

During the Week 4 study visit, a pill count will be conducted. Blood samples will be drawn to measure product concentration at DOT visit #3, Week 2, and Week 4.

Injection Phase

Adherence to study injectable product will be assessed by participants' receipt of additional injections, as administered by clinic staff.

4.5 Acceptability

Acceptability has been conceptualized as individuals' willingness and ability to use a product over time and, when available, in the context of a range of alternative choices.²³⁻²⁵ In both the fields of HIV prevention and contraception, individuals' decisions to initiate use of a product, and their ability to adhere to and sustain use of that product is strongly influenced by their knowledge and beliefs about the product, attitudes towards and experiences of product attributes and how product use fits their social/sexual context – especially in comparison to other prevention methods. As apparent from recent microbicide and PrEP clinical trials, product-related acceptability is also intertwined with the clinical trial context, including their understanding of the study product efficacy (which may be a placebo), attitudes towards other trial requirements and beliefs about the clinical trial's mission and goals. Such factors may lead to differences between within-trial acceptability and likelihood of using a product outside of a trial context.

Acceptability of an HIV prevention injectable will be assessed through brief questionnaires, assessed at four time points and two to three focus group discussions (FGDs), conducted between weeks 44 and 76.

Acceptability Questionnaires

Questionnaires, including domains regarding participant knowledge and beliefs related to injections, adherence to oral run-in, perceived advantages and disadvantages of injections, and injection attributes, will be administered to all study participants during four study visits (Weeks 0, 4, 28 and 44). Specific domains for acceptability questionnaires will include but not be limited to:

- 1) Knowledge and beliefs related to HIV prevention injection
 - Attitudes towards injections (perceived efficacy; non-reversibility; perceived effect of partial completion of doses on efficacy)
 - HIV risk perception
 - Previous experience with preventive injections for contraception, vaccinations
- 2) Advantages and disadvantages of an HIV prevention injection
 - Ease of use relative to other methods (perceived ability to take a daily pill or receive a bi-monthly injection)
 - Discretion, partner disclosure
 - Perceived safety and effectiveness relative to other prevention methods
- 3) Attributes of injection
 - Dosing – quantity and timing (preferences for higher dose less frequently, or lower dose more frequently)
 - Location of injection (issues of privacy and preferences for type/gender of providers)
 - Side effects, experienced or perceived (pain, local or systemic side effects, including headache, rash, gastrointestinal effects, dizziness)
- 4) Implications of clinical trial context on acceptability
 - Attitudes towards other clinical trial requirements (i.e., contraceptive requirement, economic/social burden of trial follow-up, access to free product and/or medical care)
 - Trust/mistrust in clinical trial mission (i.e., belief that the trial may lead to a product that benefits the community or, conversely, that it will not be made available to their community; concern that the injection may actually contain HIV)
 - Likely to use injectable outside clinical trial context

Focus Group Discussions

A subset of participants will be invited to participate in FGDs after completing the active phase of trial participation (between Weeks 44-76). FGDs will not occur during the study visits; they will be scheduled separately. FGDs will be audio-recorded and written transcripts will be generated. A maximum of three FGDs will be conducted, with at least one FGD at a US and one at an African site. The FGDs will explore in greater depth participants' attitudes towards and experiences with the injectable product they were assigned, including ease of use; perceived efficacy; side effects; the impact of the clinical trial environment on acceptability; potential stigma; relative advantages and disadvantages of an HIV prevention injectable in comparison to other HIV prevention methods.

4.6 Concomitant Medications

With the exception of medications listed in the SSP Manual as prohibited, enrolled study participants may use concomitant medications during study participation. Whenever a concomitant medication or study treatment is initiated or a dose changed, IoRs must review the concomitant medication's and study treatment's most recent package inserts, or updated information from DAIDS to obtain the most current information on drug interactions, contraindications, and precautions.

All concomitant medications, including prescribed and over-the-counter preparations, vitamins and nutritional supplements, recreational drugs, and herbal preparations reported within the 56 days prior to study enrollment and throughout the course of the study will be recorded on a Case Report Form (CRF) designated for that purpose.

5.0 PHARMACOKINETICS

Sampling Rationale

Blood samples for PK plasma analysis will be collected at study visits: DOT Visit #3, Weeks 0, 2, 4, 6, 8, 12, 14, 20, 28, 36, 44, 52, 64 and 76. Study visits were selected based on the primary safety objectives of the study. Sampling for secondary PK objectives (drug concentrations) was chosen to coincide with highly informative pre-injection times (Weeks 4, 12, 20, 28, 36 and 44) during the study which indicate the lowest concentrations during each dosing period. Week 52 sampling provides the same pre-dose concentration prior to a theoretical seventh injection (not included in this study). The sample at Week 0 will provide baseline data. The samples at DOT Visit #3 and Week 2 will assess concentration during the oral run-in period. The sample prior to the first injection (Week 4) is to assess concentration at the end of the oral dosing period which is needed to interpret the concentrations in the injection period. Samples collected at Weeks 6 and 8 will provide information about the rise to concentration peak after the Week 4 injection. The sample collected at Week 14 will provide information about the rise to concentration peak after the Week 12 injection. Samples collected at Weeks 64 and 76 will provide terminal elimination decay data for parent and metabolite at the end of dosing.

Cervicovaginal and rectal fluid samples will be collected at Week 36 (preferred) or Week 44 to assure collection after attainment of steady-state to indicate the accumulation of drug during the study.

Vaginal tissue sampling will occur once in a small subset of approximately 24 participants at US sites (Tissue Subset) to minimize impact on recruiting. Tissue collection will occur at either Week 36 (preferred) or Week 44 to assure collection after attainment of steady-state to indicate the accumulation of drug during the study. In combination with several other completed and ongoing intensive PK sampling studies, this sparse sampling data will provide key information regarding 1200 mg doses every eight weeks.

Samples to be Collected

Blood samples will be collected for PK analysis as stated above and outlined in Appendix I.

Cervicovaginal fluid and rectal fluid sampling will be conducted from participants on one occasion at either Week 36 (preferred) or Week 44.

Vaginal tissue sampling will, necessarily, be limited to a subset of approximately 24 women from the US sites, where the capacity and regulatory environment for sampling is feasible. Vaginal tissue sampling will occur on one occasion at either Week 36 (preferred) or Week 44.

Analyses to be Performed

All samples will be analyzed for TMC278 and metabolites. Plasma samples will be used to describe the pre-dose TMC278 drug concentrations, and drug concentrations over time during both the oral and injectable dosing phases. The rate of TMC278 decline from Week 52 through Week 76 will also be assessed. Cervicovaginal fluid, vaginal tissue, and rectal fluid samples collected at Week 36 (preferred) or Week 44 will be used to describe concentrations of TMC278 in the sampled anatomic compartments that would represent trough (pre-dose) concentrations well into what is anticipated to be the steady-state period. TMC278 parent to metabolite ratios in each anatomic compartment will also be described. In addition, pharmacogenomic analysis of the expression of drug metabolizing enzymes and drug transporters will also be assessed through deoxyribonucleic acid (DNA) genotyping of Enrollment blood samples and measurement of messenger ribonucleic acid (mRNA) and protein expression in tissue samples.

TMC278, metabolite, and TMC278:metabolite ratios will be reported using descriptive statistics. Comparisons between trough concentrations at Week 12 through 52 will be made to assess time to attainment of steady-state. TMC278:metabolite ratios will be compared across anatomic compartments to describe anatomic differences in TMC278 metabolism. Expression of mRNA and metabolizing proteins and transporters will be described to assess anatomic variation in enzyme and transporter expression.

6.0 STUDY PROCEDURES

An overview of study visits and procedures is included in Appendix 1. There will be nineteen study visits: Screening, Enrollment/Randomization (Week 0), four visits for DOT (between Weeks 0 and 2), Weeks 2, 4, 6, 8, 12, 14, 20, 28, 36, 44, 52, 64 and 76. After randomization, all participants will receive a supply of capsules to take by mouth once daily with a meal. At the end of the four-week oral run-in period, all participants will receive the first injections (at Week 4). Participants will receive injections again at Weeks 12, 20, 28, 36 and 44. The remaining visits are follow-up visits (Weeks 52, 64 and 76). Detailed instructions of all study procedures are provided in the SSP Manual.

Any participant who does not take all of the oral run-in product and/or does not receive all of the study injections will continue to be followed for the entire 76-week study period.

Note that the following tests will be performed at several study visits: HIV rapid testing, pregnancy testing, urine protein, and glucose testing. These tests are listed as clinic procedures in Section 6 and Appendix I. However, sites have the option to perform these tests in the laboratory.

For additional information about the PK studies planned, please see Section 5.0 of this protocol.

6.1 Screening Visit

All participants must provide written informed consent before completing any other procedures.

The following activities will occur during the Screening visit:

Administrative and Counseling Procedures

- Conduct informed consent
- Collect locator information
- Collect demographic information
- Provide HIV risk reduction counseling
- Offer condoms and lubricant
- Provide reimbursement

Clinical Procedures

- Medical history (including concomitant medications)
- Full physical examination
- EKG
- Blood collection
- HIV rapid testing
- Urine collection
- Urine pregnancy testing
- Urine protein and glucose testing
- Vaginal swab or urine collection for STI testing

Laboratory Procedures

- Analyses to be performed on blood samples
 - HIV testing (see SSP Manual)
 - Hepatitis serology: HBSAg, HBSAb, HCAb
 - CBC with differential
 - Chemistry assessments: bilirubin, creatine phosphokinase (CPK), alkaline phosphatase, creatinine, ALT, AST, total protein, glucose, calcium, phosphorous
 - Additional chemistry assessments: potassium, magnesium (Screening visit only)
 - Syphilis testing
 - Plasma storage
- Analyses to be performed on vaginal swab or urine samples
 - STI testing (gonorrhea and chlamydia) using either vaginal swab or urine

HIV counseling and testing will be offered to everyone who consents to screening. Sites will follow the HIV testing algorithm for screening included in the SSP manual. If a reactive/positive result is obtained for one or more of the HIV tests, the woman is not eligible for the study; in those cases, additional testing to confirm HIV infection will be performed in accordance with local guidelines. If HIV infection is confirmed, participants will receive counseling and be referred for appropriate care.

If all laboratory tests and interview screening indicate that an individual is eligible for the study, she will be asked to return to the site for Enrollment. Those who are not eligible

will be informed that they do not meet the requirements of the study and, if necessary, will be referred for appropriate medical care. There must be no more than 28 days between Screening and Enrollment.

Women who do not meet eligibility criteria because of an abnormal EKG, risk factors for TdP, an STI (GC, CT, or syphilis) present at Screening or report of an STI (GC, CT, or syphilis) in the past 6 months, or a history of arrhythmia may not be re-screened. Women who present at Screening with symptoms consistent with an acute HIV infection or who have a reactive HIV test may not be re-screened. Women who do not meet eligibility criteria for the study for any other reason may be re-screened at a future date at the discretion of the site IoR.

6.2 Week 0 Visit (Enrollment)

Final eligibility determination and randomization/enrollment must be completed within 28 days from the time of the first blood draw for the Screening HIV test. Participants must be present at the study site for Enrollment and randomization. All participants must have provided informed consent for the study before initiating Enrollment visit procedures. If all inclusion/exclusion criteria are met, then the participant may be enrolled. Participants with one or more reactive/positive HIV test results are not eligible for the study (see SSP Manual). The effective point of Enrollment is randomization.

The following activities will occur during the Enrollment visit:

Administrative and Counseling Procedures

- Confirm eligibility
- Confirm locator information
- Collect baseline Acceptability data
- Provide HIV risk reduction counseling
- Provide oral product adherence counseling
- Randomization*
- Offer condoms and lubricant
- Provide reimbursement

Clinical Procedures

- Interim medical history (including concomitant medications)
- Symptom-directed physical examination
- Blood collection
- HIV rapid testing
- Urine collection
- Urine pregnancy testing
- Urine protein and glucose testing
- Dispense study product for the oral run-in*
- Observe participant take oral study product with a meal provided by the site

*All HIV test results from Screening and the HIV rapid test performed at the Enrollment visit must be reviewed prior to randomization or provision of study product. If additional HIV test results from the Enrollment visit are available at this visit, those results must also be reviewed prior to randomization or provision of study product. If any of the test results are positive/reactive, the participant is not eligible for Enrollment/Randomization and should not receive study product (see SSP Manual). In those cases, additional

testing to confirm HIV infection will be performed in accordance with local guidelines. If HIV infection is confirmed, participants will receive counseling and be referred for appropriate care. The pregnancy test result from the Enrollment visit must also be confirmed to be negative prior to randomization or administration of study product.

Laboratory Procedures

- Analyses to be performed on blood samples
 - HIV testing (see SSP Manual)
 - CBC with differential
 - Chemistry assessments: bilirubin, CPK, alkaline phosphatase, creatinine, ALT, AST, total protein, glucose, calcium, phosphorous
 - Plasma storage
 - Additional plasma storage for PK testing and related assessments
 - Blood storage for genetic testing

6.3 DOT Visits #1, 2, 3 and 4

Participants will return to the study site approximately four times between the Week 0 Enrollment Visit and Week 2 Oral Run-in Safety Visit, so that study staff can directly observe participants taking the oral study product. DOT visits 1 and 2 ideally will occur during the first week post-Enrollment but no specific timing is required. DOT visits 3 and 4 ideally will occur during the second week post-enrollment but no specific timing is required.

Administrative and Counseling Procedures

- Review HIV test results from the Enrollment visit*
- Adherence assessment and pill count (done during a minimum of 2 DOT visits)
- Provide oral product adherence counseling
- Offer condoms and lubricant
- Provide reimbursement

Clinical Procedures

- Observe participant take oral study product with a meal provided by the site*

* If any HIV test results from the Enrollment visit were not available for review at the time of the Enrollment visit, they must be reviewed at one of these visits, as soon as they are available. If any of the test results are positive/reactive, the participant should not receive any additional study product (see SSP Manual).

6.3.1 DOT Visit #3

The below activities will occur only at DOT Visit #3, in addition to those listed above:

Administrative and Counseling Procedures

- Confirm locator information
- Provide HIV risk reduction counseling

Clinical Procedures

- Interim medical history (including concomitant medication and query for any side effects of oral rilpivirine)
- Symptom-directed physical examination

- AE assessment
- Blood collection
- HIV rapid testing
- Urine collection
- Urine pregnancy testing
- Urine protein and glucose testing

Laboratory Procedures

- Analyses to be performed on blood samples
 - HIV testing (see SSP Manual)
 - CBC with differential
 - Chemistry assessments: bilirubin, CPK, alkaline phosphatase, creatinine, ALT, AST, total protein, glucose, calcium, phosphorous
 - Plasma storage
 - Additional plasma storage for PK testing and related assessments

6.4 Week 2 Visit (Oral Run-in Safety Visit)

Two weeks after the Enrollment visit, participants will return to the clinic. They will specifically be asked about any side effects; a skin exam will be done to assess for rash. A pill count will be conducted. Information will be collected on how many pills were not taken and reasons for not taking pills.

Administrative and Counseling Procedures

- Confirm locator information
- Provide HIV risk reduction counseling
- Adherence assessment and pill count
- Provide oral drug adherence counseling
- Offer condoms and lubricant
- Provide reimbursement

Clinical Procedures

- Query for side effects and examine skin to assess for rash
- Observe participant take oral study product with a meal provided by the site
- Interim medical history (including concomitant medication and query for any side effects of oral rilpivirine)
- Symptom-directed physical examination
- AE assessment
- Blood collection
- HIV rapid testing
- Urine collection
- Urine pregnancy testing
- Urine protein and glucose testing

Laboratory Procedures

- Analyses to be performed on blood samples
 - HIV testing (see SSP Manual)
 - CBC with differential
 - Chemistry assessments: bilirubin, CPK, alkaline phosphatase, creatinine, ALT, AST, total protein, glucose, calcium, phosphorous
 - Plasma storage

- Additional plasma storage for PK testing and related assessments

6.5 Week 4 Visit (First Injection)

The following activities will occur during the Week 4 visit:

Administrative and Counseling Procedures

- Confirm locator information
- Collect Acceptability data
- Provide HIV risk reduction counseling
- Adherence assessment and pill count
- Provide counseling regarding the study product injections
- Offer condoms and lubricant
- Provide reimbursement

Clinical Procedures

- Interim medical history (including concomitant medication and query for any side effects of oral rilpivirine)
- Symptom-directed physical examination
- AE assessment
- EKG*
- Blood collection
- HIV rapid testing*
- Urine collection
- Urine pregnancy testing*
- Urine protein and glucose testing
- Provide 1st study injections*
- Dispense post-injection memory aid

Laboratory Procedures

- Analyses to be performed on blood samples
 - HIV testing (see SSP Manual)*
 - CBC with differential
 - Chemistry assessments: bilirubin, CPK, alkaline phosphatase, creatinine, ALT, AST, total protein, glucose, calcium, phosphorous
 - Plasma storage
 - Additional plasma storage for PK testing and related assessments

*NOTES:

- All blood samples must be collected prior to injection.
- Study product will NOT be administered if the participant has a reactive/positive HIV test result(s) from any study visit. All HIV test results from all previous study visits must be available for review at this visit. Results from the HIV rapid test performed at this visit must also be available prior to provision of the injection. If any additional HIV test results from this visit are available at this visit, those results must also be reviewed prior to injection (see SSP Manual).

- Study product will NOT be administered if the participant is pregnant. This must be based on pregnancy test results from previous visits and on the result of the urine pregnancy test performed at this visit.
- EKG must be completed and QTcF assessed PRIOR to injection. No study product will be administered to participants with QTcF > 500 ms or a change of > 60 ms from the baseline EKG conducted at Screening. See Section 7.2.5 of the Protocol, Abnormal QTcF.

NOTE: Participants who present with Grade 2 or greater RELATED AEs during the oral-run in phase will not receive the injectable TMC278 LA. Participants who present with Grade 3 or 4 UNRELATED AEs will not proceed to the injectable phase unless approved by the CMC.

The assessment of AEs at this visit (Week 4 visit) does not include review of results from the hematology and chemistry testing from this visit. Those results will not be available before the first injection is given.

6.6 Weeks 6 and 8 Visits (Post-Injection #1 Safety Visits)

The following activities will occur during the Week 6 and the Week 8 visits:

Administrative and Counseling Procedures

- Confirm locator information
- Provide HIV risk reduction counseling
- Offer condoms and lubricant
- Provide reimbursement

Clinical Procedures

- Interim medical history (including concomitant medication)
- Symptom-directed physical examination
- AE assessment
- Blood collection
- HIV rapid testing
- Urine collection
- Urine pregnancy testing
- Urine protein and glucose testing
- Review memory aid given to participant at last injection (Week 6 only)
- Examine IS

Laboratory Procedures

- Analyses to be performed on blood samples
 - HIV testing (see SSP Manual)
 - CBC with differential
 - Chemistry assessments: bilirubin, CPK, alkaline phosphatase, creatinine, ALT, AST, total protein, glucose, calcium, phosphorous
 - Plasma storage
 - Additional plasma storage for PK testing and related assessments

6.6.1 Week 6: Screening Visit for the Tissue Subset Only (US Sites)

For participants who are interested in participating in the Tissue Subset, the below activities will occur in addition to those listed above.

The following activities will occur at the Week 6 Visit or any later scheduled study visit prior to the planned vaginal tissue sampling Visit, at Week 36 (preferred) or Week 44, so that the results are available prior to the biopsy:

Administrative and Counseling Procedures

- Conduct informed consent for the Tissue Subset study
- Schedule Pap test (if indicated and documentation of satisfactory Pap results is not available); this testing will be done locally

Clinical Procedures

- Blood collection for coagulation testing*

Laboratory Procedures

- Analyses to be performed on blood samples
 - Coagulation testing: prothrombin time/international normalized ratio (PT/INR) and activated partial thromboplastin time (aPTT)*

***NOTE:**

- Blood collection and coagulation testing can be done at Week 6 or later, as long as results are available prior to enrolling into the Tissue Subset.

6.6.2 Week 8: Pap Test Visit for the Tissue Subset Only (US sites)

For participants who are interested in participating in the Tissue Subset, the below activities will occur in addition to those listed above.

The following activities will occur at the Week 8 Visit or any later scheduled study visit prior to the planned vaginal tissue sampling Visit, at Week 36 (preferred) or Week 44, so that the results are available prior to the biopsy:

Clinical Procedures

- Pap test (if indicated)

6.7 Weeks 12, 20 and 28 Visits (Injection Visits), Week 14 Visit (Post-Injection Visit)

The following activities will occur during the Week 12, 20 and 28 visits:

Administrative and Counseling Procedures

- Confirm locator information
- Collect Acceptability data (Week 28 only)
- Provide HIV risk reduction counseling
- Provide counseling regarding the study product injections
- Offer condoms and lubricant
- Provide reimbursement

Clinical Procedures

- Interim medical history (including concomitant medications)
- Symptom-directed physical examination
- AE assessment
- EKG*
- Blood collection
- HIV rapid testing
- Urine collection
- Urine pregnancy testing
- Urine protein and glucose testing
- Review memory aid given to participant at last injection (Week 28 only)
- Examine IS
- Provide study injections*
- Dispense post-injection memory aid

Laboratory Procedures

- Analyses to be performed on blood samples
 - HIV testing (see SSP Manual)
 - CBC with differential
 - Chemistry assessments: bilirubin, CPK, alkaline phosphatase, creatinine, ALT, AST, total protein, glucose, calcium, phosphorous
 - Plasma storage
 - Additional plasma storage for PK testing and related assessments

*NOTES:

- All blood samples must be collected prior to injection.
- Study product will NOT be administered if the participant has a reactive/positive HIV test result(s) from any study visit. All HIV test results from all previous study visits must be available for review at this visit. Results from the HIV rapid test performed at this visit must also be available prior to provision of the injection. If any additional HIV test results from this visit are available at this visit, those results must also be reviewed prior to injection (see SSP Manual).
- Study product will NOT be administered if the participant is pregnant. This must be based on pregnancy test results from previous visits and on the result of the urine pregnancy test performed at this visit.
- EKG must be completed and QTcF assessed PRIOR to injection. No study product will be administered to participants with QTcF > 500 ms or a change of > 60ms from the baseline EKG conducted at Screening. See Section 7.2.5 of the Protocol, Abnormal QTcF.

NOTE: Participants who present with Grade 2 or greater AEs RELATED to study product will not be given an injection. Participants who present with Grade 3 or 4 UNRELATED AEs will not be given an injection unless approved by the CMC.

The assessment of AEs at these visits (Weeks 12, 20 and 28) does not include review of results from the hematology and chemistry testing from these visits. Those results will not be available before the injections are given.

6.7.1 Week 12: Enrollment Visit for the Tissue Subset Only (US sites)

For women interested in participating in the Tissue Subset, and who are eligible for it, the below activities will occur in addition to those listed above.

The following activities will occur at the Week 12 Visit or any later scheduled study visit prior to the planned vaginal tissue sampling Visit, at Week 36 (preferred) or Week 44, so that the results are available prior to the biopsy:

Administrative and Counseling Procedures

- Review results of coagulation and Pap test results, if indicated (documentation of prior Pap results, or results obtained after the Week 6 visit).
- Review history to ensure participant has not missed injection visits.
- Review urine pregnancy results from prior visits and the urine pregnancy test result from this visit.
- If coagulation is normal, Pap test results are normal, urine pregnancy results from prior visits and the urine pregnancy test result from this visit are negative, and the participant has not missed injections then enroll in the Tissue Subset.

6.7.2 Week 14: Post-Injection #2 Safety Visit

The following activities will occur during the Week 14 visit:

Administrative and Counseling Procedures

- Confirm locator information
- Provide HIV risk reduction counseling
- Offer condoms and lubricant
- Provide reimbursement

Clinical Procedures

- Interim medical history (including concomitant medication)
- Symptom-directed physical examination
- AE assessment
- Blood collection
- HIV rapid testing
- Urine collection
- Urine pregnancy testing
- Urine protein and glucose testing
- Review memory aid given to participant at last injection
- Examine IS

Laboratory Procedures

- Analyses to be performed on blood samples
 - HIV testing (see SSP Manual)
 - CBC with differential

- Chemistry assessments: bilirubin, CPK, alkaline phosphatase, creatinine, ALT, AST, total protein, glucose, calcium, phosphorous
- Plasma storage
- Additional plasma storage for PK testing and related assessments

6.8 Weeks 36 and 44 Visits (Injection Visits)

The following activities will occur during the Week 36 and the Week 44 visits:

Administrative and Counseling Procedures

- Confirm locator information
- Collect Acceptability data (Week 44 only)
- Provide HIV risk reduction counseling
- Provide counseling regarding the study product injections
- Offer condoms and lubricant
- Provide reimbursement

Clinical Procedures

- Interim medical history (including concomitant medications)
- Symptom-directed physical examination
- AE assessment
- EKG*
- Blood collection
- HIV rapid testing
- Urine collection
- Urine pregnancy testing
- Urine protein and glucose testing
- Cervicovaginal and rectal fluid collection (Week 36 (preferred) or Week 44; for women in the Tissue Subset, fluid collection will occur at the same visit as the vaginal biopsy is conducted*)
- Review memory aid given to participant at last injection
- Examine IS
- Provide study injections*
- Dispense post-injection memory aid

Laboratory Procedures

- Analyses to be performed on blood samples
 - HIV testing (see SSP Manual)
 - CBC with differential
 - Chemistry assessments: bilirubin, CPK, alkaline phosphatase, creatinine, ALT, AST, total protein, glucose, calcium, phosphorous
 - Plasma storage
 - Additional plasma storage for PK testing and related assessments
 - Cervicovaginal fluid and rectal fluid processing and storage

***NOTES:**

- All blood and fluid samples must be collected prior to injection.

- Fluid samples will NOT be collected if the participant is pregnant. This must be based on pregnancy test results from previous visits and on the result of the urine pregnancy test performed at this visit.
- Study product will NOT be collected if the participant has a reactive/positive HIV test result(s) from any study visit. All HIV test results from all previous study visits must be available for review at this visit. Results from the HIV rapid test performed at this visit must also be available prior to provision of the injection. If any additional HIV test results from this visit are available at this visit, those results must also be reviewed prior to injection (see SSP Manual).
- Study product will NOT be administered if the participant is pregnant. This must be based on pregnancy test results from previous visits and on the result of the urine pregnancy test performed at this visit.
- EKG must be completed and QTcF assessed PRIOR to injection. No study product will be administered to participants with QTcF > 500 ms or a change of > 60 ms from the baseline EKG conducted at Screening. See Section 7.2.5 of the Protocol, Abnormal QTcF.

NOTE: Participants who present with Grade 2 or greater AEs RELATED to study product will not be given an injection. Participants who present with Grade 3 or 4 UNRELATED AEs will not be given an injection unless approved by the CMC.

The assessment of AEs at these visits (Weeks 36 and 44) does not include review of results from the hematology and chemistry testing from these visits. Those results will not be available before the injections are given.

6.8.1 Week 36: Biopsy Visit for the Tissue Subset Only (US sites)

For women enrolled in the Tissue Subset, the following activities will occur at one visit (either Week 36 (preferred) or Week 44), in addition to those listed above:

Administrative Procedures

- Review study product injection history

Clinical Procedures

- Vaginal tissue collection

Laboratory Procedures

- Vaginal tissue processing and storage

NOTES:

- Tissue samples must be collected prior to injection.
- Tissue samples will not be collected if the participant has missed any injections.

- Tissue samples will NOT be collected if the participant is pregnant. This must be based on pregnancy test results from previous visits and on the result of the urine pregnancy test performed at this visit.
- Tissue samples will NOT be collected if the participant has a reactive/positive HIV test result(s) from any study visit. All HIV test results from all previous visits must be available for review at this visit. Results from the HIV rapid test performed at this visit must also be available prior to provision of the injection. If any additional HIV test results from this visit are available at this visit, those results must also be reviewed prior to injection (see SSP Manual).
- STI samples may be collected if participant is pregnant at the discretion of the site clinician.

6.9 Week 52 (Primary Outcome Visit) and Weeks 64 and 76 Visits (Tail Phase Visits)

The following activities will occur during the Week 52, 64 and 76 visits:

Administrative and Counseling Procedures

- Confirm locator information
- Provide HIV risk reduction counseling
- Offer condoms and lubricant
- Provide reimbursement

Clinical Procedures

- Interim medical history (including concomitant medications)
- Symptom-directed physical examination
- AE assessment
- Blood collection
- HIV rapid testing
- Urine collection
- Urine pregnancy testing
- Urine protein and glucose testing
- Review memory aid given to participant at last injection (Week 52 only)
- Examine IS (Week 52 only)

Laboratory Procedures

- Analyses to be performed on blood samples
 - HIV testing (see SSP Manual)
 - CBC with differential
 - Chemistry assessments: bilirubin, CPK, alkaline phosphatase, creatinine, ALT, AST, total protein, glucose, calcium, phosphorous
 - Plasma for storage
 - Additional plasma storage for PK testing and related assessments

The assessment of AEs at these visits (Weeks 52, 64 and 76) does not include review of results from the hematology and chemistry testing from these visits.

6.10 HIV Confirmation Visit

Additional procedures required for women who have any reactive or positive HIV test during the study (see Appendix I). These procedures must be performed on a separate date (typically within two to three weeks of the first reactive/positive HIV test).

Administrative and Counseling Procedures

- Confirm locator information
- Provide HIV counseling
- Offer condoms and lubricant

Clinical Procedures

- Blood collection
- HIV rapid testing

Laboratory Procedures

- Analyses to be performed on blood samples
 - HIV testing (see SSP Manual)
 - CD4 cell count
 - HIV viral load
 - HIV resistance testing*
 - Plasma for storage (see Appendix I)

All participants with confirmed HIV infection will be provided ART for the period of 12 months. See Section 6.11, HIV Seroconversion.

* Samples may be collected and sent for resistance testing at a local laboratory to assist with clinical management. Results from resistance testing performed in local laboratories will not be reported to the SDMC. Stored plasma may not be used for this testing.

Note: If a participant has signs or symptoms consistent with acute HIV infection, testing will be performed using an HIV RNA test. Regardless of whether HIV RNA testing is used for diagnostic testing, HIV infection must be confirmed in all cases using two independent samples collected on different days.

6.11 HIV Seroconversion

Frequent testing for HIV acquisition during the study period will help prevent dosing with the injectable product in an HIV-infected participant, minimizing the risk that resistant virus will emerge. Therefore, HIV testing will be performed at the majority of scheduled study visits. In addition, if a participant has signs or symptoms consistent with acute HIV infection, or expresses a concern about recent HIV acquisition, testing will be performed using an RNA test that, in the opinion of the site IoR, is able to detect early HIV infection. If possible, the site should select an assay that is US FDA-cleared for early HIV diagnosis such as the Aptima HIV-1 RNA Qualitative Assay. Regardless of whether HIV RNA testing is used for diagnostic testing, HIV infection must be confirmed in all cases using two independent samples collected on different days.

At the Screening and Enrollment visits, individuals will be deferred and referred for evaluation and care if they have any signs or symptoms consistent with acute (pre-

seroconversion) HIV infection, or if they express a concern about recent HIV infection. Signs and symptoms consistent with acute HIV infection include fever (temperature >38°C), pharyngitis or a new rash. Evaluation of possible acute HIV infection prior to enrollment will be performed outside of the study, according to local testing guidelines.

Participants who have any reactive or positive HIV test result during follow-up visits will have further testing to confirm infection, as described in the SSP Manual. HIV infection must be confirmed in all cases using two independent samples. Samples from participants with confirmed HIV infection may be sent to a local laboratory for resistance testing to assist with clinical management; results from resistance testing performed in local laboratories will not be reported to the SDMC. The participant will not receive additional doses of study product, even if further testing indicates that they do not have HIV infection.

For enrolled participants with suspected or confirmed HIV infection, site staff should follow the procedures outlined in Appendix I and the SSP Manual. The treatment assignment will remain blinded; however, an IoR can request unblinding if necessary for the treatment of the participant's HIV infection.

If a participant seroconverts during the study, PDS will provide funding support for ART to be locally procured by the site for the period of one year (equivalent to 5 half-lives of TMC278 LA) to prevent persistent-monotherapy-related resistance complications. At the end of the year, participants will be transitioned to a local HIV care clinic where ART provision could be continued (if the participant desires to stay on ART).

In addition, if a participant requests PEP for HIV exposure, she will either be offered PEP on site (depending on site capability) or she will be referred to an appropriate clinic. If the participant starts PEP, she should not receive any additional doses of study product (oral or injectable) until completion of the course of PEP, and documentation of a negative HIV test result. Participants should receive HIV testing at least 14 days after completion of PEP treatment. HIV negative results must be documented before resuming study product. Refer to the SSP Manual for HIV testing requirements following completion of PEP treatment.

Resistance testing will be performed retrospectively for all participants who acquire HIV infection during the study, regardless of study arm (see Section 10.2). If real-time resistance testing is needed for clinical management, that testing will be arranged by the site outside of the study.

6.12 Clinical Management of Pregnancy

Because this dose of product is investigational, receipt of study product by biologically female study participants requires the use of an effective method of contraception, including an IUD, hormonal contraception, implants, or sterilization. All participants should also use male or female condoms for prevention of HIV and other STIs. As needed, study staff will provide contraceptive counseling to enrolled participants throughout the duration of study participation and will facilitate access to contraceptive services through direct service delivery and/or active referrals to local service providers. Study staff also will provide participants with male and/or female condoms and counseling on use of condoms.

Pregnancy testing will be performed at Screening, Enrollment, and at the majority of scheduled follow-up visits. Participants will be encouraged to report all signs or symptoms of pregnancy to study staff. Participants who are pregnant will no longer receive study product (oral or injectable) but will continue to be followed according to the schedule of visits for 24 weeks after discontinuation. The site IoR or designee will counsel any participants who become pregnant regarding possible risks to the fetus according to site-specific SOPs. Participants may not enroll if they are currently breastfeeding and study product should be discontinued if any participant identifies that she is breastfeeding after enrollment. The IoR or designee also will refer the participant to all applicable services; however, sites will not be responsible for paying for pregnancy-related care.

If a participant reports a desire to become pregnant during the study, she will no longer receive study product or placebo (oral or injectable).

Participants who are pregnant at the Week 76 visit will continue to be followed until the pregnancy outcome is ascertained or it is determined that the pregnancy outcome cannot be ascertained. Pregnancy outcomes will be reported on relevant CRFs. Outcomes meeting criteria for expedited adverse event (EAE) reporting also will be reported. After the pregnancy outcome, women who are not breastfeeding will be given the option to continue dosing if they are within the 40 week dosing period established by the date of the Enrollment visit.

If a participant becomes pregnant, she is not eligible for enrollment in the Tissue Subset component of this study.

6.13 Clinical Management of an STI

Should a participant test positive for syphilis, GC, and/or CT after enrollment she will be provided appropriate medical treatment. She will be retained in the study.

7.0 SAFETY MONITORING AND ADVERSE EVENT REPORTING

7.1 Safety Monitoring

Close cooperation between the Protocol Chairs, study site IoRs, NIAID Medical/Program Officer, NIAID Pharmacist, LOC CRM, SDMC Biostatistician, SDMC Clinical Affairs Associate, PDS, and other study team members will be necessary in order to monitor participant safety and respond to occurrences of toxicity in a timely manner. This group is the HPTN 076 CMC. The CMC will correspond by email and will hold conference calls as needed during the period of study implementation.

The study site IoRs are responsible for continuous close monitoring of all AEs that occur among study participants, and for alerting the rest of the protocol team if unexpected concerns arise. **Accrual and injectable product use will be suspended if two or more participants in the injection phase experience the same Grade 3 or higher AE judged to be related to study product.** The Study Monitoring Committee (SMC) and Medical Officer then will review all pertinent safety data and determine whether to continue accrual and product use. A decision to stop the trial may be made by the

protocol team at this time, or at any such time that the team agrees that an unacceptable type and/or frequency of AEs has been observed.

The HPTN SMC will review safety data periodically and communicate any concerns to the study team.

7.2 Adverse Event Definitions and Reporting Requirements

Requirements, definitions and methods for expedited reporting of AEs are outlined in Version 2.0 of the DAIDS EAE Manual (or latest version), which is available on the RSC website at <http://rsc.tech-res.com/safetyandpharmacovigilance/>. This information is also available in the HPTN Manual of Operations (MOP) posted online at <http://www.hptn.org>.

7.2.1 Adverse Event

An AE is defined as any untoward medical occurrence in a clinical research participant administered an investigational product and which does not necessarily have a causal relationship with the investigational product. As such, an AE can be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the product.

Study participants will be provided a 24-hour telephone number and instructed to contact the study clinician to report any AEs they may experience. For life-threatening events, they will also be instructed to seek immediate emergency care. Where feasible and medically appropriate, participants will be encouraged to seek evaluation where the study clinician is based, and to request that the clinician be paged or otherwise contacted upon their arrival. With appropriate permission of the participant, whenever possible records from all non-study medical providers related to AEs will be obtained and required data elements will be recorded on study CRFs. All participants reporting an AE will be followed clinically, until the AE resolves (returns to baseline) or stabilizes.

Study site staff will document in source documents and the appropriate AE Log CRF all AEs reported by or observed in enrolled study participants regardless of severity and presumed relationship to study product. AE severity will be graded per the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009).

Relatedness is an assessment made by a study clinician of whether or not the event is related to the study agent. The relationship of all AEs to study product will be assessed as specified in Version 2.0 of the DAIDS EAE Reporting Manual (or latest version).

For each trial participant, the AE reporting period begins at Enrollment and ends when the participant completes the Week 76 or early exit Visit.

7.2.2 Serious Adverse Event

An SAE will be defined per US Code of Federal Regulations (CFR) 312.32 and International Conference on Harmonization (ICH), "Good Clinical Practice: Consolidated Guidance" (E6) and "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting" (E2A), as AE occurring at any dose that:

- Results in death,

- Is life-threatening,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect,
- Requires inpatient hospitalization or prolongation of existing hospitalization.

This includes important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed above.

Per ICH SAE definition, hospitalization itself is not an AE, but is an outcome of the event. The following types of hospitalization do not require expedited reporting to DAIDS:

- Any admission unrelated to an AE (e.g. for labor/delivery, cosmetic surgery, administrative, or social admission for temporary placement for lack of place to sleep),
- Protocol-specified admission (e.g. for procedure required by protocol),
- Admission for diagnosis or therapy of a condition that existed before receipt of study agent(s) and has not increased in severity or frequency as judged by the clinical investigator.

7.2.3 EAE Reporting to DAIDS

Requirements, definitions and methods for expedited reporting of AEs are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at <http://rsc.tech-res.com/safetyandpharmacovigilance/>.

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov or from within the DAERS application itself.

Sites where DAERS has not been implemented will submit expedited AEs by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website: <http://rsc.tech-res.com/safetyandpharmacovigilance/>. For questions about EAE reporting, please contact the RSC (DAIDSRSCSafetyOffice@tech-res.com).

The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study. The study agents for the purposes of EAE reporting are outlined in Section 4.1. According to the SAEs reporting category in the manual, all SAEs occurring during the study reporting period will be reported to the DAIDS RSC Safety Office in an expedited manner, within three reporting days of site awareness of the events.

After Week 76 or early exit, only suspected unexpected serious adverse drug reactions (SUSARs; defined in Version 2.0 of the DAIDS EAE Manual) that study staff become aware of on a passive basis (from publicly available information) will be reported to DAIDS in an expedited manner.

7.2.4 Injection Site Evaluation

As specified in Appendix I, an evaluation of the IS for pain and skin reactions will be performed at Weeks 6, 8, 12, 14, 20, 28, 36, 44 and 52.

Preferably, all IS reactions will be read and interpreted by one and the same qualified person at each site. All IS reactions will be recorded on a CRF.

7.2.5 Abnormal QTcF

Participants with a QTcF > 500 ms and/or an increase in QTcF from baseline of > 60 ms must have a confirmatory measurement, preferably within 48 hours after the EKG results have become available.

If the QTcF > 500 ms and/or the increase in QTcF from baseline of > 60 ms are confirmed, intake of study product (oral or injectable) must be permanently discontinued. Participants will continue to be followed.

The event leading to discontinuation must be reported as an AE.

7.3 Social Impacts Reporting

Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social impacts may result (*i.e.*, because participants could be perceived as being HIV-infected or at "high risk" for HIV infection). For example, participants could be treated unfairly, or could have problems being accepted by their families and/or communities. Social impacts that are judged by the IoR/designee to be serious or unexpected will be reported to the responsible site's IRBs/ECs at least annually, or according to their individual requirements. Social impacts will be collected and reported on CRFs during regular visits. In the event that a participant reports a social impact, every effort will be made by study staff to provide appropriate care and counseling to the participant, and/or referral to appropriate resources for the safety of the participant. Each site will provide such care and counseling in accordance with standardized guidance in the SSP Manual. While maintaining participant confidentiality, study sites may engage their Community Advisory Boards (CABs) in exploring the social context surrounding instances of social harm, to minimize the potential occurrence of such impact.

8.0 STATISTICAL CONSIDERATIONS

8.1 Overview and Summary of Design

This is a multi-site, double-blinded, two-arm, randomized, placebo-controlled trial to evaluate the safety, acceptability, tolerability, and pharmacokinetics of the injectable TMC278 LA product given once every eight weeks over a 40 week period among sexually active, HIV-uninfected women ages 18-45. A total of approximately 132 eligible women will be enrolled and randomized with the TMC278 LA: placebo ratio of two:one resulting in 88 women in the TMC278 LA arm and 44 women in the placebo arm.

Approximately 96 women will be enrolled in SSA (64 and 32 in the TMC278 LA and placebo arm, respectively) and approximately 36 women will be enrolled in the US (24 and 12 in the TMC278 LA and placebo arm, respectively).

Total study duration is expected to be 100 weeks. Accrual will require approximately 24 weeks. After Enrollment, participants will receive four weeks of once daily oral rilpivirine (25 mg capsules) or oral placebo. Upon completion of the oral run-in period, participants will receive six injection sets of either TMC278 LA or placebo at eight week intervals over 40 weeks. After the injection period, participants will be followed for 32 more weeks. The total study duration for each participant is 76 weeks.

8.2 Study Endpoints

8.2.1 Primary Endpoint

Consistent with the primary study objective to evaluate the safety of the injectable product, TMC278 LA, (1200 mg dose administered at Weeks 4, 12, 20, 28, 36 and 44), through 48 weeks after initial injection (at Week 52) in women in SSA and US, the primary safety endpoint is the proportion of participants in each arm experiencing any Grade 2 or higher clinical and laboratory AEs that occur from the initial injection to 8 weeks after the last injection (Week 52) among participants who receive at least one injection. Clinical and laboratory AEs are defined by the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, Dec 2004.

8.2.2 Secondary Endpoints

Consistent with the secondary objective to examine study product acceptability, the following endpoint will be assessed:

- The proportion of participants who would be interested in using the study product for HIV prevention in the future.

Consistent with the secondary objective to assess tolerability of study product, the following endpoint will be assessed:

- The proportion of participants who do not receive the full regimen of study injections, in accordance with the protocol.

Consistent with the secondary objective to describe the PK of TMC278 LA in plasma, the following endpoints will be assessed:

- Parent/metabolite concentration in plasma.
- Time to steady-state of TMC278 LA in plasma.
- Pre-dose (trough) concentrations at steady state in plasma.
- Apparent terminal elimination rate of TMC278 LA in plasma.

Consistent with the secondary objective to describe TMC278 LA concentration in cervicovaginal fluid and rectal fluid in participants, and in vaginal tissue in a subset of approximately 24 participants (US sites only), the following endpoint will be assessed:

- Parent/metabolite concentration in cervicovaginal fluid, rectal fluid, and vaginal tissue.

Blood, fluids and tissue samples will be collected for PK analysis as outlined in Appendix I. Blood will be collected at Enrollment and visits at DOT #3 and Weeks 2, 4, 6, 8, 12, 14, 20, 28, 36, 44, 52, 64 and 76.

Cervicovaginal fluid and rectal fluid will be collected at all sites from participants at one of the following visits: Week 36 (preferred) or 44. Vaginal tissue will be collected at sites in the US that have the capacity for these procedures from a subset of approximately 24 participants at one of the following study visits: Week 36 (preferred) or Week 44.

Consistent with the secondary study objective evaluating the safety of rilpivirine (oral + injectable LA product) through Week 76 in women in SSA and US, the secondary safety endpoint is the proportion of women in each arm who experienced Grade 2 or higher clinical and laboratory AEs through Week 76.

Consistent with the secondary objective to estimate HIV incidence through 76 weeks of study duration, the secondary endpoint is the number of participants acquiring HIV infections during study follow-up in each arm.

8.3 Primary Study Hypothesis

HPTN 076 hypothesizes that TMC278 LA 1200 mg (formulation G001) will be safe and well-accepted.

8.4 Sample Size and Power Calculations

8.4.1 Primary Safety Endpoint

The proposed total sample size of the study is approximately 132 women randomized in a two:one ratio to TMC278 LA arm and the placebo arm respectively. Counting for ten percent LTFU per year, we expect approximately 120 women (80 in the TMC278 LA arm and 40 women in the placebo arm) will be followed for 48 weeks after the initial injection. A two:one randomization was selected to increase the precision on estimation of acceptability and PK characteristics of TMC278 LA.

The goal of the safety evaluation for this study is to identify safety concerns associated with the administration of the injectable TMC278 LA product. The ability of this study to detect SAEs (See Section 7.2.2) can be expressed by the true event rate above which at least 1 SAE would likely be observed and the true event rate below which no events would likely be observed. Specifically, for TMC278 LA arm ($n=80$), there is a 90% chance of observing at least 1 event if the true rate of such an event is 2.9% or more and there is a 90% chance of observing no events if the true rate is 0.1% or less.

The probabilities of observing zero, one or more, and two or more AEs among the 80 women who receive at least one injection of TMC278 LA are shown in Table 2 given a range of possible true adverse event rates. These calculations provide a more complete picture of the sensitivity of this study design to identify potential safety concerns with the injectable TMC278 LA product.

Table 2. Probabilities of observing 0, 1 or more, and 2 or more events among the women in the TMC278 LA arm for different true event rates.

True Event rate	P(0 events n=80)	P(≥ 1 event n=80)	P(≥ 2 events n=80)
0.5%	67.0%	33.0%	6.1%
1.0%	44.8%	55.2%	19.1%
2.5%	13.2%	86.8%	59.7%
5%	1.7%	98.3%	91.4%
10%	<0.1%	>99.9%	99.8%
15%	<0.1%	>99.9%	>99.9%

The primary safety endpoint is the proportion of women experiencing Grade 2 or higher clinical and laboratory AEs from the initial injection through 48 weeks of study follow-up after the initial injection (at Week 52) in each arm. The precision with which the true event rate can be estimated from the observed data depends on the true underlying event rate and the sample size. Table 3 shows two-sided 95% confidence intervals (CIs) for the true event rate based on various possible observed rates, given the sample size of 80 women in the TMC278 LA arm. Calculations are done using the score test method.²⁶

Table 3. Two-sided 95% CIs for the true event rate given possibly observed event rates in the TMC278 LA arm (n=80).

N	Observed Event Rate (%)	95% Asymptotic CI for True Event Rate (%)
80 women in TMC278 LA arm (n=80)	0	(0, 4.2)
	2.5	(0.7, 8.2)
	5	(2, 11.7)
	10	(5.3, 18)
	15	(9, 23.9)
	20	(13, 29.5)
	25	(17.1, 35)
	0	(0, 4.2)
	2.5	(0.7, 8.2)

The primary objective of the study is to evaluate the safety of the injectable TMC278 LA product administered at eight weeks interval over 40 weeks. The numbers presented in Table 4 are the minimum true proportion of women who experience the safety event of interest in the TMC278 LA arm given the possible true proportion of women experiencing that event in the placebo arm such that the study has 80% or 90% statistical power to distinguish the different proportions between the two arms. These calculations use a Fisher's exact 2-sided test with a Type I error rate of 0.05. For either 80% or 90% power, the sizes of differences that the study is powered to detect are fairly large indicating that the study has a limited power for a formal comparison between the two arms. Therefore the formal comparison between the two arms is not listed as the primary objective.

Table 4. Power for comparison of the proportions of women who experience the safety endpoints between the two arms.

Rate in the Placebo Arm	Minimum True Rate in the TMC278 LA Arm	
	90% power	80% power
2.5% (=1/40)	23%	20%
5% (=2/40)	28%	25%
10% (=4/40)	36%	32%
15% (=6/40)	44%	40%
20% (=8/40)	50%	46%
25% (=10/40)	57%	52%

8.4.2 Secondary Endpoints

Acceptability Endpoint

To evaluate the acceptability of the injectable TMC278 LA product using a questionnaire, at Weeks 0, 4, 28, and 44, the proportion of participants at each of the four time points, who will be interested in using the study product in the future, will be calculated for participants in the TMC278 LA arm.

Table 5 shows the two-sided 95% CI for the true acceptability percentage given a particular observing acceptability percentage among the women in the TMC278 LA arm (n=80). Calculations are done using the score test method.²⁶

Table 5. The two-sided 95% CIs for the true acceptability/tolerability percentage given a particular observed acceptability/tolerability percentage in the TMC278 LA arm (n=80).

Observed Acceptability/Tolerability Percentage	95% CI for true acceptability/intolerability percentage
50	(39.3, 60.7)
60	(49, 70)
70	(59.2, 78.9)
80	(70, 87.3)
90	(81.5, 94.8)
100	(95.4, 100)

Tolerability Endpoint

To evaluate tolerability, the proportion of participants who do not receive the full regimen of injections due to an AE will be calculated for the women in the TMC278 LA product arm. Based on Table 5, if the observed tolerability is 90%, the 95% CI will be 81.5% to 94.8%.

Pharmacokinetic Endpoints

One of the PK endpoints is a description of the distribution of trough TMC278 LA concentrations at Week 36, or 44 in blood, cervicovaginal fluid, and rectal fluid among the women in the TMC278 LA arm. Assuming a log-normal distribution, Table 6 shows the 90% CI for the geometric mean of the trough level achieved with a sample size of 80 participants receiving TMC278 LA, assuming a range of means and Coefficient of Variations (CVs).

Table 6. Two-sided 90% CI for the geometric mean of the trough level.

Geometric mean trough concentration (ng/mL)	CV ¹	90% CI
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40	0.2	(34.9, 45.9)
	0.4	(30.4, 52.6)
	0.6	(26.5, 60.4)
50	0.2	(43.2, 57.8)
	0.4	(37.4, 66.9)
	0.6	(32.3, 77.4)
60	0.2	(51.5, 69.9)
	0.4	(44.2, 81.4)
	0.6	(38.0, 94.8)
70	0.2	(59.8, 82.0)
	0.4	(51.0, 96.0)
	0.6	(43.6, 112.5)
80	0.2	(68.0, 94.2)
	0.4	(57.7, 110.9)
	0.6	(49.0, 130.5)
90	0.2	(76.1, 106.4)
	0.4	(64.4, 125.8)
	0.6	(54.5, 148.7)

1. CV for the log transformed data.

HIV Incidence Rate

The HIV incidence rate in each arm will be estimated. The precision with which the true HIV incidence rate can be estimated from the observed data depends on the length of follow-up period and the sample size. Two-sided 95% CIs for the true HIV incidence rate in each arm based on observing a particular numbers of HIV infections in each arm over the 76 week study duration are shown in Table 7. Calculations are done using Poisson rate CI calculation method.²⁷

Table 7. Estimated HIV incidence rate and 95% CIs based on observing a particular number of HIV infections in each arm during the 76 weeks study duration.

# conversions during study follow-up	The TMC278LA Arm (n=88)	The Placebo Arm (n=44)
0	0 (0, 2.79)	0 (0, 5.59)
1	0.76 (0.02, 4.22)	1.52 (0.04, 8.44)
2	1.52 (0.18, 5.47)	3.03 (0.37, 10.95)
3	2.27 (0.47, 6.64)	4.55 (0.94, 13.28)
4	3.03 (0.83, 7.76)	6.06 (1.65, 15.52)
5	3.79 (1.23, 8.84)	7.58 (2.46, 17.68)

8.5 Participant Accrual, Follow-up, and Retention

A total of 132 women will be enrolled in approximately 24 weeks. After randomization, participants will receive four weeks of once daily oral rilpivirine (25 mg capsules) or placebo, followed by six injections of TMC278 LA or placebo at Weeks 4, 12, 20, 28, 36 and 44 and will be followed up for additional 32 weeks. The total follow-up period for each participant is 76 weeks. Each site will target an annual retention rate of 90% of enrolled participants over the 76 week follow-up period.

8.6 Randomization

The eligible participants will be randomized to one of the two study arms with the TMC278 LA and the placebo ratio of 2:1. Study arm randomization will be stratified by site and done in blocks to ensure balanced assignment for products at each site and across arms.

The randomization scheme will be generated and maintained by the HPTN SDMC. Additional details regarding the process of randomization will be included in the SSP Manual.

8.7 Blinding

Participants and study site staff (except for site pharmacists) will be blinded to the randomization assignments. Blinding will be maintained until all data are entered into the study database, and all study endpoint data and other data included in the final analysis has been cleaned and verified and the data are ready for final analysis. Selected staff at the HPTN LC may request to be unblinded prior to analysis of plasma, fluid and/or tissue samples to avoid the unnecessary time and expense of performing analysis on samples from participants who received placebo.

As noted in Section 6.11, an IoR can request unblinding for in the event a participant seroconverts during the study, and unblinding would assist in the treatment of the participant's HIV infection. If an IoR feels that specific product knowledge is necessary to protect participant safety, the IoR will notify the LOC CRM. The CRM will contact the Protocol Chairs, study site IoRs, NIAID Medical/Program Officer, SDMC Biostatistician, SDMC Clinical Affairs Associate, and other study team members as appropriate to review the request.

8.8 Data Analysis

8.8.1 Study Monitoring Committee

Data and Safety Monitoring Board (DSMB) oversight is not planned for the study. The HPTN SMC will conduct interim reviews of study progress, including rates of participant accrual, visit retention, completion of primary and main secondary endpoint assessments, data collection or lab issues, and, in a closed report, safety data by arm.

8.8.2 Primary Analyses

When the use of descriptive statistics to assess group characteristics or differences is required, the following methods will be used: for categorical variables, the number and percent in each category; for continuous variables, the mean, median, standard deviation, quartiles and range (minimum, maximum). Within-treatment group assessment of the change from the baseline measurement to a follow-up measurement will be analyzed using McNemar test (for categorical response variables) or the paired t-test or Wilcoxon signed-ranks test (for continuous variables). When use of formal testing to assess differences between users of the placebo arm and users of TMC278 LA is required, the following methods will be used: for binomial response variables, chi-square tests and logistic regression (or exact testing methods); for continuous variables, t-tests and linear regression or nonparametric methods if data are non-Normal.

To assess the adequacy of the randomization, participants in each of the two arms will be compared for baseline characteristics including demographics and laboratory measurements using descriptive statistics.

Safety Endpoints

The primary safety analysis will include Grade 2 or higher clinical and laboratory events that occur from the initial injection to 8 weeks after the final injection (Week 52) among participants who receive at least one injection. In an extended safety analysis, all data from enrolled participants will be analyzed according to the initial randomization assignment regardless of how many injections they receive.

To assess safety, the number and the percentages of participants experiencing each safety endpoint will be tabulated by study arm. Each participant will contribute once in each category (i.e., only for the highest severity AE for each participant) for the calculation of event rates. Two-sided 95% CIs will be calculated for each safety endpoint for each arm using the score test method²⁶. Fisher's exact test will be used to test for differences in event rates between the two arms. No formal multiple comparison adjustments will be employed for safety endpoints.

Injection Site Reaction

The number and percentage of participants experiencing each type of IS reaction sign or symptom will be tabulated by severity. For a given sign or symptom, each participant's IS reaction will be counted once under the maximum severity for all injection visits.

AEs

AEs will be tabulated using MedDRA preferred terms. The number and percentage of participants experiencing each specific AE will be tabulated by severity and by relationship to study product. For the calculations in these tables, each participant's AEs will be counted once under the maximum severity or the strongest relationship to study product. AEs will be summarized for those that are treatment related during LA dosing separately from those that are treatment related during oral dosing and also for those that are treatment related across the entire study follow-up (combining both LA and oral dosing).

A listing of SAEs reported to the DAIDS RSC Safety Office will provide details of the events including severity, relationship to study product, time between onset and last injection, number of injections received, and a summary of the event.

8.8.3 Secondary Analyses

Acceptability

To assess acceptability of the study product at Weeks 0, 4, 28, and 44, the percentage (with 95% CI) of participants, who report they are interested in using the TMC278 LA product as PrEP in the future, will be calculated among those in the study product arm, and will be compared with the percentage in the placebo arm.

Tolerability

To assess tolerability, the number and the percent of participants who will not complete the injections due to AE will be tabulated by study arm. Chi-square test will be used to compare the proportion of participants who terminated from receiving the full course of injections due to an AE between the two study arms.

Pharmacokinetics

Descriptive statistics will be used to characterize trough plasma concentrations in the sampled anatomic compartments. Either mean and standard deviation, or median and interquartile range (IQR) will be computed depending on the distribution of the endpoints. Time to steady state will be assessed by comparing plasma concentration at week 4 (post-oral, pre-injection baseline) to all the subsequent visits through Week 52.

Differences in metabolizing enzymes and parent drug to metabolite ratios among sample matrices (e.g., plasma, fluids, tissue) will be explored. Similarly, correlations between parent-metabolite ratios and metabolizing enzyme expression will also be explored. Terminal elimination decay rate will be simulated from Week 52, 64, and 76 concentrations.

For additional information about the PK studies, please see Section 5.0 of this protocol.

HIV incidence rate

HIV incidence rate will be calculated as the total number of participants with confirmed HIV infections divided by the person-years of follow-up in each arm. CIs will be calculated based on Poisson distribution assumptions.

9.0 HUMAN SUBJECTS CONSIDERATIONS

9.1 Ethical Review

This protocol and the template ICF(s) contained in Appendix III — and any subsequent modifications — will be reviewed and approved by the HPTN Scientific Review Committee and DAIDS Prevention Science Review Committee (PSRC) with respect to scientific content and compliance with applicable research and human subjects regulations.

The protocol, site-specific ICF, participant education and recruitment materials, and other requested documents — and any subsequent modifications — also will be reviewed and approved by the ethical review bodies responsible for oversight of research conducted at the study site.

Subsequent to initial review and approval, the responsible IRBs/ECs will review the protocol at least annually. The IoR will make safety and progress reports to the IRBs/ECs at least annually, and within three months of study termination or completion. These reports will include the total number of participants enrolled in the study, the number of participants who completed the study, all changes in the research activity, and all unanticipated problems involving risks to human subjects or others. Study sites will submit documentation of continuing review to the DAIDS Protocol Registration Office (PRO), in accordance with the current DAIDS Protocol Registration Policy and Procedure Manual.

9.2 Informed Consent

Written informed consent will be obtained from each study participant. Each study site is responsible for developing a study ICF for local use, based on the template in Appendix

III, which describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations. The study site also is responsible for translating the template form into local languages, and verifying the accuracy of the translation by performing an independent back-translation.

Literate participants will document their provision of informed consent by signing their ICFs. Non-literate participants will be asked to document their informed consent by marking their ICFs (e.g., with an X, thumbprint, or other mark) in the presence of a literate third party witness. (Further details regarding DAIDS requirements for documenting the informed consent process with both literate and non-literate participants are provided in the DAIDS SOP for Source Documentation.) Any other local IRB/EC requirements for obtaining informed consent from non-literate persons also will be followed.

Participants will be provided with a copy of their ICFs if they are willing to receive them.

9.3 Risks

Phlebotomy

Phlebotomy may lead to discomfort, feelings of dizziness or faintness, and/or bruising, swelling and/or infection.

Stress surrounding HIV Testing

Participants may become embarrassed, worried, or anxious when completing their HIV risk assessment and/or receiving HIV counseling. They also may become worried or anxious while waiting for their HIV test results. Trained counselors will be available to help participants deal with these feelings.

Study Drug-Related Risks

Rash

It is possible that participants will develop a rash. No participants exposed to TMC278 or TMC278 LA have developed Stevens Johnson Syndrome.

Acute Systemic Allergic Reaction

It is possible that a participant may have a systemic allergic reaction to either oral rilpivirine or to the TMC278 LA nano-suspension.

General Side Effects

It is possible that after taking rilpivirine or TMC278 LA, a participant could experience dizziness, insomnia, somnolence, and/or abnormal dreaming. Should this occur, participants will be advised not to operate machinery or drive a vehicle. Participants may also have a headache, feel tired, or have a dry mouth. It is also possible that a participant could experience a side effect not yet attributed to TMC278 LA.

Gastrointestinal Side Effects

It is possible that participants may have abdominal pain, nausea, vomit, or diminished appetite.

Hepatic Side Effects

It is possible that a participant may develop elevated transaminase levels. We will monitor ALT and AST at the beginning and then throughout the

study. Participants will be told by study staff if any harmful changes in liver function are detected. Study product may be withheld.

Depression

Depressive disorders have been noted with use of rilpivirine.

Fat Redistribution

Changes in distribution and accumulation of body fat have been observed during use of ART.

Injection Site Reactions

It is possible that participants will develop IS reactions such as localized pain, tenderness to palpation, itching, swelling, bruise, redness or other color, and/or inflammation (e.g., warm sensation, pulsing sensation).

Resistance to Rilpivirine or TMC278 LA

It is possible that a participant who becomes HIV infected in this study may develop viral resistance mutations to rilpivirine or TMC278 LA during this study. Resistance could occur at any time during the study. Resistance could occur during the oral run-in period if a participant does not consistently take the rilpivirine given to her and seroconverts during the oral run-in. Resistance could also occur during the tail phase post injection of TMC278 LA, when drug concentrations are low, if a woman acquires HIV infection during this time.

Tissue Biopsy

For the subset of approximately 24 participants in the US from whom a vaginal tissue biopsy will be obtained at either the Week 36 (preferred) or Week 44 visit, there is risk of hemorrhage or infection. Some participants may find the procedure uncomfortable. It is also possible that participants may become embarrassed while vaginal tissue is collected.

Fluid Collection

Participants may become embarrassed while fluids are collected from the vagina and rectum. Some participants may find the procedure uncomfortable.

Confidentiality breach

Although study sites make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social impacts may result.

9.4 Benefits

There may be no direct benefits to participants in this study, however, participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may lead to the development of a safe and effective injectable PrEP.

In addition, participants will receive HIV counseling and testing as part of the study, as well as medical exams and EKGs. Participants also will be screened for a number of STIs, and provided STI treatment if applicable.

Participants who acquire HIV infection during the study will continue to be followed in

this study. ART will be provided for the period of 12 months to any participant who seroconverts. See Section 6.11, HIV Seroconversion.

9.5 Incentives

Pending IRB/EC approval, participants will be compensated for their time and effort in this study, and/or be reimbursed for travel to study visits and time away from work. Site-specific reimbursement amounts will be specified in the study ICFs.

9.6 Confidentiality

All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with access limited to study staff. All laboratory specimens, reports, study data collection, process, and administrative forms will be identified by a coded number only to maintain participant confidentiality. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.

Participant's study information will not be released without the written permission of the participant, except as necessary for monitoring by the NIAID and/or its contractors; representatives of the HPTN LOC, SDMC, and/or LC; the US Food and Drug Administration, other government and regulatory authorities, and/or site IRBs/ECs. IoRs also will allow inspection of all study-related documentation by authorized representatives of PDS and/or its contractors after consultation with DAIDS about scheduling.

A Federal Certificate of Confidentiality will be sought for the US sites participating in this study. The Certificate will apply only to US study sites, and will protect study staff from being compelled to disclose study-related information by any Federal, State or local civil, criminal, administrative, legislative, or other proceedings.

9.7 Communicable Disease Reporting Requirements

Study staff will comply with all applicable local requirements to report communicable diseases identified among study participants to local health authorities. Participants will be made aware of all reporting requirements during the study informed consent process.

9.8 Study Discontinuation

The study also may be discontinued at any time by NIAID, the HPTN, and/or the US Food and Drug Administration, other government or regulatory authorities, and/or site Ministries of Health (MOHs)/IRBs/ECs.

10.0 LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT

Laboratory procedures are described below, in Appendix I and Section 6.0.

10.1 Local Laboratory Specimen Processing

As described in Section 6, the following types of specimens will be collected for testing at the Local Laboratory (LL):

- HIV rapid testing ^a
- Urine pregnancy testing ^a
- Urine protein and glucose testing
- HIV testing (see SSP Manual)
- Hematology testing (CBC with differential)
- Chemistry testing (see Appendix I)
- Syphilis testing
- Hepatitis testing
- STI testing (vaginal swab or urine)
- Coagulation testing (Tissue Subset only; US sites only)
- Pap test (Tissue Subset only; US sites only, as indicated)
- HIV viral load
- CD4 cell count
- HIV resistance testing at a local laboratory (for clinical management)
- Plasma storage
- Additional plasma storage for PK testing
- Cervicovaginal fluid processing and storage.
- Rectal fluid processing and storage
- Vaginal tissue processing and storage (Tissue Subset, only at US sites)

^aHIV rapid testing, pregnancy testing, and urine testing for protein and glucose may be performed in the clinic or in the laboratory.

Pregnancy testing

All women of reproductive potential will have a urine β HCG test for pregnancy (sensitivity of ≤ 25 mIU/mL) at the majority of visits. Continued pregnancy testing is not required following an initial positive test result. It will be repeated after pregnancy completion and must have returned to normal prior to recommencement of study product.

STI testing

STI testing will be performed on all participants at Screening, using either vaginal swabs or urine.

The expectation is that STI testing will be performed locally. Sites should contact the HPTN LC if local testing is not possible. Sites should also contact the HPTN LC for approval if they plan to use an alternate laboratory for testing. This testing should be performed according to local standard of care.

Coagulation Testing

Coagulation testing will be done at Week 6 or later for the subset of women at the US sites who are interested in participating in the Tissue Subset. Coagulation testing (PT/INR and aPTT) will be done locally using blood samples. Results must be available prior to Tissue Subset Enrollment. Women who have abnormal coagulation test results will not be eligible to participate in the Tissue Subset.

Pap testing

Pap testing, if indicated, will be scheduled at the Week 6 visit or later for the subset of women at the US sites who are interested in participating in the Tissue Subset and who do not have documentation of satisfactory Pap results in the 12 calendar months prior to tissue sampling. Pap testing will be done locally. Results must be available prior to Tissue Subset Enrollment. Women who have abnormal Pap test results will not be eligible to participate in the Tissue Subset.

General procedures

Each study site will adhere to standards of good clinical laboratory practice, the HPTN MOP, the SSP Manual, and local SOPs for proper collection, processing, labeling, transport, and storage of specimens to the LL. Specimen collection, testing, and storage at the LL will be documented using the HPTN Laboratory Data Management System (LDMS) as described in the SSP Manual.

All specimens will be shipped in accordance with International Air Transport Association (IATA) specimen shipping regulations. All shipments will be documented using the HPTN LDMS as described in the SSP Manual.

10.2 HPTN Laboratory Center Specimen Processing

As described in Section 6, and indicated in Appendix I, plasma will be stored at every visit at which HIV testing is performed. This plasma may be requested by the HPTN LC for Quality Assurance (QA) and other assessments.

Virology

The HPTN LC will perform QA testing, including testing to determine HIV infection status in selected cases. Additional assays may be performed at the HPTN LC or at an outside laboratory designated by the HPTN LC. This testing will include HIV drug resistance testing for all participants who acquire HIV infection. The following tests may also be performed for participants who acquire HIV infection: HIV subtyping, and other tests to characterize HIV viruses and/or the host response to HIV infection. Results will not be returned to the sites or study participants, with the exception noted below.

Resistance testing will be performed at the HPTN LC or a laboratory designated by the HPTN LC. This testing will be performed retrospectively at the end of the study. If real-time resistance testing is needed for clinical management, that testing should be arranged by the site outside of the study; separate specimens should be collected for that testing. For sites that do not have the capacity for local resistance testing for clinical care, results from resistance testing may be provided at the end of the study at the request of the site IoR, with approval of the HPTN LC and Protocol Chair. Results from specialized resistance testing (e.g., minority variants analysis, if performed) will not be returned to study sites.

Pharmacology

Plasma samples will be collected for TMC278 and metabolite assessment at the Week 0 visit for baseline analysis; at the DOT #3, Week 2 visit and Week 4 visit (following the oral dosing period); and at the Week 6, 8, 12, 14, 20, 28, 36, 44, 52, 64 and 76 visits. These samples will be collected from all participants, although PK testing may be limited to a subset of the samples.

Cervicovaginal fluid (all women) and rectal fluid (all women) will be collected at either Week 36 (preferred) or Week 44 for pharmacologic assessment. Vaginal tissue will be collected from a subset of approximately 24 participants in the US (Tissue Subset) at either Week 36 (preferred) or Week 44 for pharmacologic assessment.

Plasma, tissue, and luminal fluid will be processed and frozen locally for subsequent shipment to the HPTN LC following procedures outlined in the SSP Manual. Measurement of TMC278 and metabolites will be performed at the HPTN LC or at an outside laboratory designated by the HPTN LC. The primary pharmacologic assessments will be performed using assays that have been validated and approved by the Clinical Pharmacology Quality Assurance (CPQA) Committee. Results will not be returned to the sites or study participants.

Stored plasma may also be tested for the presence of TMC278 or other ARV drugs or other substances in any research participant.

Pharmacogenomics

Blood samples collected for pharmacogenomic testing will be analyzed for genetic polymorphisms associated with study product exposure. Assays will be performed at the HPTN LC. Results will not be returned to the sites or study participants.

*Note that samples for pharmacokinetics and pharmacogenomics may be unblinded in the Pharmacology Laboratory (only), so the relevant assays are only performed on participant samples with respect to study product assignment.

10.3 Quality Control and Quality Assurance Procedures

Study sites will document that their laboratories are certified under the Continuous Laboratory Improvement Act of 1988 (CLIA-certified) and/or participate in DAIDS-sponsored External Quality Assurance (EQA) programs, or other QA methods as deemed appropriate by the HPTN LC. LC staff will conduct periodic visits to each site to assess the implementation of on-site laboratory quality control (QC) procedures, including proper maintenance of laboratory testing equipment and use of appropriate reagents. LC staff will follow up directly with site staff to resolve any QC or QA problems identified through proficiency testing and/or on-site assessments. Throughout the course of the study, the HPTN LC will select a random sample of stored specimens to test for QA purposes. LC staff will follow-up directly with site staff to resolve any QA problems identified through this process.

10.3.1 QC for HIV Diagnostic Testing

Before performing HIV diagnostic testing, all sites must validate their HIV testing procedures, and the validation studies must be approved by the HPTN LC. Local laboratories or clinics will perform testing for HIV diagnosis at Screening, Enrollment, and other study visits. Algorithms for HIV diagnostic testing are provided in the SSP Manual.

Throughout the course of the study, the HPTN LC will select a random sample of stored specimens to test for QA purposes. The total number of specimens undergoing QA testing will follow the QA processes as described in the HPTN MOP.

The LC will inform site staff of the samples selected for QA testing, and site staff will ship the selected specimens to the LC. The LC will test the specimens for evidence of HIV infection and compare the results of their tests with the results obtained by the local labs. LC staff will follow-up directly with site staff to resolve any QA problems identified through this process.

10.3.2 Quality Assurance for Local Laboratory/Clinic testing

Local laboratories will perform chemistry, hematology, urinalysis, hepatitis, STI, and pregnancy testing as indicated in Appendix I. Non-US laboratories performing these tests will be monitored by Patient Safety Monitoring and International Laboratory Evaluation (pSMILE) and must demonstrate successful participation in the relevant EQA programs. US sites should send these tests to CLIA-certified laboratories and must participate in EQA programs.

10.3.3 Quality Assurance for CD4 Cell Count Testing

Local laboratories may also perform CD4 cell count testing as indicated in Appendix I. Non-US laboratories performing these tests will be monitored by the DAIDS Immunology Quality Assurance (IQA) program and UNKEQAS program and must demonstrate successful participation in these programs. US sites must use CLIA-certified laboratories; participation in the IQA program is recommended.

10.3.4 Quality Assurance for HIV RNA Testing

Local laboratories may also perform HIV RNA/viral load testing as indicated in Appendix I. Non-US laboratories performing these tests will be monitored by the DAIDS Virology Quality Assurance (VQA) program and must demonstrate successful participation in this program. US sites must use CLIA-certified laboratories; participation in the VQA program is recommended.

10.4 Specimen Storage and Possible Future Research Testing

Study sites will store specimens collected in this study at least through the end of the study. In addition, study participants will be asked to provide written informed consent for these samples to be stored after the end of the study for possible future non-protocol listed testing; after review and approval of HPTN leadership. The specimens of participants who do not consent to long-term storage and additional testing will be destroyed at the end of the study.

10.5 Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the US CDC. All infectious specimens will be transported in accordance with US regulations (42 CFR 72).

11.0 ADMINISTRATIVE PROCEDURES

11.1 Protocol Registration

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent form(s) approved, as appropriate, by their local IRB/EC and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific ICFs *WILL* be reviewed and approved by the DAIDS PRO and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICF(s) *WILL NOT* be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

11.2 Study Activation

Pending successful protocol registration and submission of all required documents, LOC staff will “activate” the site to begin study operations. Study implementation may not be initiated until a study activation notice is provided to the site.

11.3 Study Coordination

NIH is the sponsor of the study. PDS holds the IND application for this study (#11944). Copies of all regulatory documents submitted to this IND by DAIDS will be forwarded to PDS for cross-referencing with Janssen's other INDs for the study product. Assignment of all sponsor responsibilities for this study will be specified in a Clinical Trials Agreement executed by PDS and HPTN.

Study implementation will be directed by this protocol as well as the SSP manual. The SSP manual — which will contain electronic links for the *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials*, as well as the DAIDS Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2.0, dates January 2010 and the DAIDS Toxicity Tables — will outline procedures for conducting study visits; data and forms processing; AE assessment, management and reporting;

dispensing study products and documenting product accountability; and other study operations.

Study CRFs and other study instruments will be developed by the protocol team and HPTN SDMC. Data will be transferred to the HPTN SDMC for data entry, cleaning, reporting and analysis. Quality control reports and queries will be generated and distributed to the study sites on a routine schedule for verification and resolution.

Close coordination between protocol team members will be necessary to track study progress, respond to queries about proper study implementation, and address other issues in a timely manner. Rates of accrual, adherence, follow-up, and AE incidence will be monitored closely by the team as well as the HPTN SMC. The Protocol Chairs, DAIDS Medical Officer, Protocol Biostatistician, SDMC Project Manager, and LOC CRM will address issues related to study eligibility and AE management and reporting as needed to assure consistent case management, documentation, and information-sharing across sites.

11.4 Study Monitoring

On-site study monitoring will be performed in accordance with DAIDS policies. Study monitors will visit the site to:

- verify compliance with human participants and other research regulations and guidelines;
- assess adherence to the study protocol, study-specific procedures manual, and local counseling practices; and
- confirm the quality and accuracy of information collected at the study site and entered into the study database.

Site IoRs will allow study monitors to inspect study facilities and documentation (e.g., ICFs, clinic and laboratory records, other source documents, CRFs), as well as observe the performance of study procedures. IoRs also will allow inspection of all study-related documentation by authorized representatives of the HPTN LOC, SDMC, LC, NIAID, and US and in-country government and regulatory authorities. IoRs also will allow inspection of all study-related documentation by authorized representatives of PDS and/or its contractors after consultation with DAIDS about scheduling. A site visit log will be maintained at the study site to document all visits.

11.5 Protocol Compliance

The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the Protocol Chair and DAIDS Medical Officer. All protocol amendments must be submitted to and approved by the relevant IRB(s)/EC(s) and the DAIDS RSC prior to implementing the amendment.

11.6 Investigator's Records

The IoR will maintain, and store in a secure manner, complete, accurate, and current study records throughout the study. In accordance with Federal regulations, for each of the two investigational products tested, the IoR will retain all study records for at least two years following the date of marketing approval for the study product for the indication

in which it was studied. If no marketing application is filed, or if the application is not approved, the records must be retained for two years after the US FDA is notified that the IND is discontinued. Study records include administrative documentation — including protocol registration documents and all reports and correspondence relating to the study — as well as documentation related to each participant screened and/or enrolled in the study — including informed consent forms, locator forms, CRFs, notations of all contacts with the participant, and all other source documents.

11.7 Use of Information and Publications

Publication of the results of this study will be governed by the HPTN MOP and policies. Any presentation, abstract, or manuscript will be submitted by the IoR to the protocol team for review, and then to the HPTN MRC for review and approval prior to submission. PDS will have the opportunity to review and comment on all presentations, abstracts and manuscripts.

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13.0 APPENDIX I: SCHEDULE OF STUDY VISITS AND PROCEDURES

Schedule I. Schedule for Routine Study Visits and Procedures

	Screening	Enroll/Randomize, *First Oral Dose Observed	DOT Visit 1	DOT Visit 2	DOT Visit 3	DOT Visit 4	Oral Run-in Safety Visit	First Injection	Post-Injection Safety Visit	Post-Injection Safety Visit	Second Injection	Post-Injection Safety Visit	Third Injection	Fourth Injection	Fifth Injection	Sixth Injection	Primary Outcome Visit	Tail Phase Visit	Tail Phase Visit
Week		0	0	0	1	1	2	4	6	8	12	14	20	28	36	44	52	64	76
Administrative and Acceptability Evaluations/Procedures																			
Obtain informed consent	X																		
Confirm eligibility		X																	
Locator information collected	X																		
Locator information confirmed		X			X		X	X	X	X	X	X	X	X	X	X	X	X	X
Demographic information collected	X																		
Acceptability data collected		X						X						X		X			
Review HIV test results from Enrollment visit ¹			X	X	X	X													
HIV risk reduction counseling	X	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X
Adherence assessment and oral study product pill count			X ¹²	X ¹²	X ¹²	X ¹²	X	X											
Oral study product adherence counseling		X	X	X	X	X	X												
Study product injection counseling								X			X		X	X	X	X			
Randomization		X																	
Offer condoms and lubricant	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Provide reimbursement	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Evaluations/Procedures																			
Complete medical history including medications	X																		
Interim medical history including concomitant meds		X			X		X	X	X	X	X	X	X	X	X	X	X	X	X
Full physical exam	X																		
Symptom-directed physical exam		X			X		X	X	X	X	X	X	X	X	X	X	X	X	X
Query for side effects and examine skin for rash							X												
AE assessment					X		X	X	X	X	X	X	X	X	X	X	X	X	X
EKG	X							X			X		X	X	X	X			
Blood collection	X	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X
HIV rapid testing ^{2,3}	X	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X
Urine collection	X	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test ^{3,4}	X	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X
Urine protein and glucose testing ³	X	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X
Vaginal swab or urine collection ⁵	X																		
Cervicovaginal and rectal fluid collection ¹¹															X				

	Screening	Enroll/Randomize, First Oral Dose Observed	DOT Visit 1	DOT Visit 2	DOT Visit 3	DOT Visit 4	Oral Run-in Safety Visit	First Injection	Post-Injection Safety Visit	Post-Injection Safety Visit	Second Injection	Post-Injection Safety Visit	Third Injection	Fourth Injection	Fifth Injection	Sixth Injection	Primary Outcome Visit	Tail Phase Visit	Tail Phase Visit
Week		0	0	0	1	1	2	4	6	8	12	14	20	28	36	44	52	64	76
Clinical Evaluations/Procedures Continued																			
Oral run-in product dispensed		X																	
Directly observed therapy for oral product		X	X	X	X	X	X												
Post-injection memory aid dispensed								X			X		X	X	X	X			
Post-injection memory aid reviewed									X			X		X	X	X	X		
Examine injection site									X	X	X	X	X	X	X	X	X		
Study drug injections								X			X		X	X	X	X			
Laboratory Evaluations/Procedures																			
HIV testing ²	X	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X
Hepatitis testing ⁶	X																		
Hematology (CBC + diff, platelets)	X	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry testing ⁷	X	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X
Potassium and magnesium	X																		
Syphilis testing	X																		
STI testing – vaginal swab or urine	X																		
Plasma storage ⁸	X	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X
Plasma storage for PK testing ⁹		X			X		X	X	X	X	X	X	X	X	X	X	X	X	X
Blood storage for genetic testing ¹⁰		X																	
Cervicovaginal and rectal fluid processing and storage ¹¹															X				

* Participants will be observed while taking the study product by site staff on approximately six occasions during the first two weeks of the oral run-in (at Week 0, at Week 2, and on four separate DOT visits between Weeks 0 and 2. DOT visits 1 and 2 will ideally occur during the first week post-Enrollment but no specific timing is required. DOT visits 3 and 4 will ideally occur during the second week post-Enrollment but no specific timing is required.

- (1) If any HIV test results from the Enrollment visit were not available for review at the time of the Enrollment visit, they must be reviewed at one of these visits, as soon as they are available. If any of the test results are positive/reactive, the participant should not receive any additional study product (see SSP Manual).
- (2) The HIV testing algorithm is provided in the SSP Manual. Participants who have one or more reactive or positive HIV test result (any assay) at Screening or Enrollment are not eligible to participate in the study, even if they are confirmed to be HIV-uninfected. Additional testing is required for participants who have a reactive or positive HIV test after enrollment (see Appendix I, Schedule III and the SSP Manual). In all cases, HIV acquisition must be confirmed using two specimens collected on different dates (see SSP Manual). HIV testing does not need to be performed after confirmation of HIV infection (based on results from samples collected on two separate dates).
- (3) HIV rapid testing, pregnancy testing, and urine dipstick testing for protein and glucose may be performed in the clinic or in the laboratory.

- (4) Pregnancy testing is not required at subsequent visits if a positive result is obtained.
- (5) Sites may perform STI testing for GC/CT at Screening using either a vaginal swab or urine sample.
- (6) Hepatitis testing will include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb) and hepatitis C antibody (HcAb) tests.
- (7) Chemistry testing will include: bilirubin, CPK, alkaline phosphatase, creatinine, ALT, AST, total protein, glucose, calcium, phosphorous.
- (8) Stored plasma will be used for Quality Assurance testing at the HPTN LC and for other assessments described in Section 10. These assessments will be performed retrospectively; results will not be returned to study sites or participants.
- (9) Additional plasma samples will be collected at the indicated visits for PK and related assessments. Different procedures for sample processing may be needed for these specimens (see SSP Manual). At Weeks 4, 12, 20, 28, 36 and 44, blood must be collected before injection of study product.
- (10) Whole blood will be stored at Enrollment for pharmacogenetic testing.
- (11) Cervicovaginal and rectal fluid collection can be done at either Week 36 (preferred) or Week 44. For participants in the Tissue Subset, fluid collection and storage must be performed at the same visit as the vaginal tissue biopsy (Week 36 (preferred) or Week 44; see Schedule II).
- (12) A pill count is to be conducted during at least 2 DOT-specific study visits.

Schedule II. Additional Procedures for the Tissue Subset

	Screening	Enroll/Randomize, First Oral Dose Observed	DOT Visit 1	DOT Visit 2	DOT Visit 3	DOT Visit 4	Oral Run-in Safety Visit	First Injection	Post-Injection Safety Visit	Post-Injection Safety Visit	Second Injection	Post-Injection Safety Visit	Third Injection	Fourth Injection	Fifth Injection	Sixth Injection	Primary Outcome Visit	Tail Phase Visit	Tail Phase Visit
Week		0	0	0	1	1	2	4	6	8	12	14	20	28	36	44	52	64	76
Administrative and Behavioral Evaluations/Procedures																			
Obtain informed consent for Tissue Subset									X										
Schedule Pap test if indicated ¹									X										
Prior to Enrollment, review coagulation and Pap test results ³											X								
Prior to Enrollment, review history to ensure participant has not missed injection visits ³											X								
Prior to Enrollment, review urine pregnancy results from prior and current visits ³											X								
Enroll in the Tissue Subset if eligible ³											X								
Review injection history ³															X				
Clinical Evaluations/Procedures																			
Blood collection for coagulation testing ³									X										
Vaginal tissue collection ^{2,4}															X				
Laboratory Evaluations/Procedures																			
Pap Test, if indicated ^{1,3,5}										X									
Coagulation testing (PT/INR, aPTT) ^{3,5}									X										
Tissue processing/storage ⁴															X				

- (1) To be offered if a satisfactory Pap smear is not documented within the last 12 calendar months and is indicated. See Section 3.1.1.
- (2) Vaginal tissue will be used for pharmacologic assessments. Vaginal tissue will be collected only at US sites that have this capacity. Collection at Week 36 is preferred but tissue may be collected Week 44.
- (3) This activity may occur at one of several visits, but must happen prior to vaginal biopsy.
- (4) These procedures must be performed on the same day, but can be done at either Week 36 (preferred) or Week 44.
- (5) Coagulation and Pap testing can also be done at later visits, but results must be available for enrollment into the Tissue Subset.

Schedule III. Schedule for Additional Laboratory Procedures for Enrolled Women who have a Reactive or Positive HIV Test Result (HIV Confirmation Visit)

	HIV Confirmation Visit
Administrative procedures	
Locator information reviewed	X
HIV counseling	X
Offer condoms and lubricant	X
Clinical procedures	
Blood collection	X
HIV rapid testing ^{1,2}	X
Laboratory procedures	
HIV testing ²	X
CD4 cell count	X
HIV viral load	X
HIV resistance testing ^{2,3}	X
Plasma storage ⁴	X

- (1) HIV rapid testing may be performed in the clinic or in the laboratory.
- (2) The HIV testing algorithm is provided in the SSP Manual.
- (3) Sites may collect specimens for resistance testing at a local laboratory to assist with clinical management; results from resistance testing performed in local laboratories will not be reported to the SDMC. Stored plasma may not be used for this testing.
- (4) Stored plasma will be used for Quality Assurance testing and other assessments described in Section 10. For participants who acquire HIV infection, these assessments will include resistance testing; additional assessments may include HIV subtyping, characterization of the virus and/or the host response to infection. These assessments will be performed retrospectively; results will not be returned to study sites or participants (with possible exception of resistance test results, as noted in Section 10).

14.0 APPENDIX II: TOXICITY MANAGEMENT

14.1 Toxicity Management General Guidance

In general, the IoR has the discretion to hold study product at any time if s/he feels that continued product use would be harmful to the participant, or interfere with treatment deemed clinically necessary according to the judgment of the IoR. IoRs should consult the CMC for further guidance in restarting study drug or progressing to permanent discontinuation. Revealing a participant's blinded status may occur only for individuals who seroconvert or in the event that knowledge of study drug is deemed critical to the management of a serious emergent medical condition of the participant. The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, dated December 2004 (with Clarification dated August 2009), (which is available at the following website: <http://rsc.tech-res.com/safetyandpharmacovigilance/>) must be followed.

If study drug is held or stopped due to toxicity, participant should have repeat clinical and laboratory evaluations as determined in the tables below, if possible, until toxicity resolves or on a schedule determined by the CMC.

Grade 1

In general, participants who develop a Grade 1 AE regardless of relatedness to study product, and that is not specifically addressed in the Tables below may continue use of the study product per protocol.

Grade 2

In general, participants who develop a Grade 2 AE unrelated to study product, and that is not specifically addressed in the Tables below may continue use of the study product per protocol.

If the Grade 2 AE occurs during the oral phase and is deemed related to study drug by the IoR, study drug must be discontinued and the CMC must be notified; the participant will not proceed to the injectable phase. If the Grade 2 AE occurs during the injection phase and is deemed related to study drug by the IoR, no additional injections will be given and the CMC must be notified.

Grades 3 and 4

In general, participants who develop a Grade 3 or 4 AE unrelated to study product during the oral run-in phase must be discontinued from the study drug and the CMC must be notified. These participants will not receive additional oral study drug or proceed to the injection phase unless approved by the CMC. Participants who develop a Grade 3 or 4 AE unrelated to study product during the injection phase will not receive the next injection unless approved by the CMC.

If a Grade 3 or 4 AE occurs during the oral phase and is deemed related to study drug by the IoR, study drug must be discontinued and the CMC must be notified; the participant will not proceed to the injectable phase. If the Grade 3 or 4 AE occurs during the injection phase and is deemed related to study drug by the IoR, no additional study drug injections will be given and the CMC must be notified.

General Criteria for Discontinuation of Study Product

Participants may voluntarily discontinue the study products for any reason at any time during the oral run-in phase. During the injection phase, participants may elect not to receive future injections. IoRs will permanently discontinue participants from study product per protocol for any of the specific criteria below, which may be further clarified in the SSP Manual. IoRs also may permanently discontinue participants from study product for use of prohibited medication (see SSP Manual), or for reasons not shown here or in the SSP Manual (e.g., to protect participants' safety and/or if participants are unable or unwilling to comply with study product use procedures). In such cases, the IoR may query the CMC for review. The CMC will provide a written response to the site indicating whether the CMC has recommended permanent discontinuation of study product based on careful review of all relevant data. It should be noted that the safety of the participant should always take precedence, and therefore, an IoR may determine that study drug be permanently discontinued before the CMC has time to respond. This is acceptable, and in such cases, the CMC should be consulted as soon as possible regarding the nature of the case and the course of action taken.

The criteria for permanent discontinuation of study product use for an individual participant are:

- Study product-related toxicity requiring permanent discontinuation of study product per the guidelines above and below
- Completion of regimen as defined in the protocol
- Request by participant to terminate study product
- Clinical reasons determined by the IoR
- New HIV infection
- Breastfeeding or lactation

Any participant who prematurely discontinues study drug should be followed according to the procedures in Appendix I, with the exception of study drug dispensation, counseling, and adherence measurements.

Study drug will be temporarily withheld from a participant for any of the following reasons:

- Report of use of prohibited concomitant medications described in the SSP Manual. Study drug use may resume when the participant reports that he is no longer taking the prohibited medication, provided other reasons for temporary study drug hold/permanent discontinuation do not apply.
- The participant is unable or unwilling to comply with required study procedures such as HIV testing and routine laboratory assessments, or otherwise might be put at undue risk to her safety and well-being by continuing study drug use, according to the judgment of the IoR. The IoR must consult the CMC on all temporary study drug holds instituted for this reason for further guidance on resuming study drug use, continuing the temporary hold, or progressing to permanent discontinuation. If study drug use is temporarily held/permanently discontinued for this reason, but the underlying reason for the temporary hold

later resolves, the IoR should consult the CMC to resume study drug use at that time.

- The participant has one or more reactive HIV test results, or expresses a concern about having acute HIV infection. Criteria for resuming use of study drug in these circumstances are defined in the SSP.
- Pregnancy. Study drug may be recommenced when participant is no longer pregnant.

Participants who temporarily or permanently discontinue study drug will be instructed to return all study drugs as soon as possible.

14.2 Guidance on Toxicity Management for Specified Toxicities:

14.2.1 Nausea, Vomiting and Diarrhea

Although common, nausea, vomiting and diarrhea following initiation of therapy with antiretroviral medication usually subsides or resolves during the first few weeks of treatment.

In most cases this can be treated symptomatically with good resolution. With intractable nausea or vomiting study product should be withheld and resumption should be discussed with the CMC.

Alternative causes for diarrhea should be sought, and if appropriate, treated symptomatically. Should intractable diarrhea be present, study product should be withheld and resumption should be discussed with the CMC.

CONDITION AND SEVERITY	IMMEDIATE ACTION	FOLLOW-UP AND MANAGEMENT
Nausea		
<p>Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake (Grade 1)</p> <p>Persistent nausea resulting in decreased oral intake for 24 – 48 hours (Grade 2, un-related)</p>	Continue study drug (reminder to take study drug with a meal during oral phase)	Treat symptomatically with hydration, oral antiemetic or antidiarrheal therapies, at the discretion of the IoR. The IoR should order any clinically relevant laboratory analyses (per judgment of the IoR).
<p>Persistent nausea resulting in decreased oral intake for 24 – 48 hours (Grade 2, related)</p> <p>Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (e.g., IV fluids) (Grade 3)</p> <p>Life-threatening consequences (e.g., hypotensive shock) (Grade 4)</p>	Discontinue study drug temporarily	Participants with Grade 2 nausea, vomiting, or diarrhea, for which an alternative etiology is not established, or Grade ≥ 3 must discontinue the study drug temporarily until Grade 1 or lower and be treated symptomatically. Should condition(s) not improve to Grade 1 within 7 days, the IoR should consult the CMC for guidance on continuing the temporary discontinuation or progressing to permanent discontinuation of study drug.
CONDITION AND SEVERITY	IMMEDIATE ACTION	FOLLOW-UP AND MANAGEMENT
Vomiting		
<p>Transient or intermittent vomiting with no or minimal interference with oral intake (Grade 1)</p> <p>Frequent episodes of vomiting with no or mild dehydration (Grade 2, un-related)</p>	Continue study drug (reminder to take study drug with a meal during oral phase)	Treat symptomatically with hydration, oral antiemetic or antidiarrheal therapies, at the discretion of the IoR. The IoR should order any clinically relevant laboratory analyses (per judgment of the IoR).
<p>Frequent episodes of vomiting with no or mild dehydration (Grade 2, related)</p> <p>Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids) (Grade 3)</p> <p>Life-threatening consequences (e.g., hypotensive shock) (Grade 4)</p>	Discontinue study drug temporarily	Participants with Grade 2 nausea, vomiting, or diarrhea, for which an alternative etiology is not established, or Grade ≥ 3 must discontinue the study drug temporarily until Grade 1 or lower and be treated symptomatically. Should condition(s) not improve to Grade 1 within 7 days, the IoR should consult the CMC for guidance on continuing the temporary discontinuation or progressing to permanent discontinuation of study drug.

CONDITION AND SEVERITY	IMMEDIATE ACTION	FOLLOW-UP AND MANAGEMENT
Diarrhea		
Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period (Grade 1) Persistent episodes of unformed to watery stools OR Increase of 4 – 6 stools over baseline per 24-hour period (Grade 2, un-related)	Continue study drug (reminder to take study drug with a meal during oral phase)	Treat symptomatically with hydration, oral antiemetic or antidiarrheal therapies, at the discretion of the IoR. The IoR should order any clinically relevant laboratory analyses (per judgment of the IoR).
Persistent episodes of unformed to watery stools OR Increase of 4 – 6 stools over baseline per 24-hour period (Grade 2, related) Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated (Grade 3) Life-threatening consequences (e.g., hypotensive shock) (Grade 4)	Discontinue study drug temporarily	Participants with Grade 2 nausea, vomiting, or diarrhea, for which an alternative etiology is not established, or Grade ≥ 3 must discontinue the study drug temporarily until Grade 1 or lower and be treated symptomatically. Should condition(s) not improve to Grade 1 within 7 days, the IoR should consult the CMC for guidance on continuing the temporary discontinuation or progressing to permanent discontinuation of study drug.

14.2.2 Clinical Hepatitis

Participants taking the study drug(s) should be monitored for the development of signs and symptoms of hepatitis which include fatigue, malaise, anorexia, nausea, dark urine and clay colored stools, bilirubinuria, jaundice, liver tenderness, or hepatomegaly, with or without initially abnormal serum or plasma transaminase levels.

Participants with these signs and symptoms should be encouraged to seek medical attention immediately and have hepatic parameters assessed. Relevant markers of viral hepatitis should also be assessed.

Careful assessments should be done to rule out the use of alcohol, lactic acidosis syndrome, non-study medication-related drug toxicity, herbal medications/supplements, or viral hepatitis as the cause of elevation in AST or ALT of any grade. If the AST/ALT elevation is considered most likely to be due to concomitant illness or medication, standard management, including discontinuation of the likely causative agent, if possible, should be undertaken. If symptoms or signs of clinical hepatitis are present, study drug must be held or discontinued in consultation with CMC. In addition, all participants with elevated values should be considered for testing for Hepatitis A, B, and C infection.

If the IoR has determined in consultation with the CMC that the case has stabilized, it may be possible to decrease the frequency of follow-up laboratory testing. Resumption of study drug will also be determined in consultation with CMC.

CONDITION AND SEVERITY	STUDY DRUG USE	FOLLOW-UP AND MANAGEMENT
Elevations in AST or ALT (New clinical finding or increase from baseline clinical finding only)		
1.25 – 2.5 x ULN (Grade 1)	Continue study drug unless participant is symptomatic	Participants may enter the study with $\leq 2 \times$ ULN transaminase elevations. If a new elevation occurs, AST or ALT should be repeated in one week. Study drug may be continued while repeating AST and ALT at the discretion of the IoR provided the participant is asymptomatic. In the case of symptomatic participants, study drug will be held temporarily, and management (including resumption of study drug) should be arranged in consultation with the CMC.
2.6 – 5.0 x ULN (Grade 2)	Continue study drug unless participant is symptomatic	Participants should have AST/ALT re-checked as soon as possible (ideally within 1 week of the receipt of the results) and then be followed weekly until levels are $\leq 2 \times$ ULN transaminase. The frequency of follow up may be altered at the discretion of the site IoR if deemed to be unrelated to study product following consultation with the CMC. Study drug may continue at the discretion of the IoR provided the participant is asymptomatic. In the case of symptomatic participants or if thought to be study drug related, study drug will be held temporarily., and management (including resumption of study drug) should be arranged in consultation with the CMC.
5.1 – 10.0 x ULN (Grade 3)	Discontinue study drug temporarily	Study drug should be temporarily held for any Grade 3 AST or ALT. Participants should have AST/ALT re-checked as soon as possible (ideally within 1 week of the receipt of the results). Participants should then be followed weekly until levels are $\leq 2 \times$ ULN transaminase. Resumption of study drug should be arranged in consultation with the CMC. If improvement to Grade ≤ 1 cannot be documented within three weeks of receiving the Grade 3 results, study drug must be permanently discontinued. If following a Grade 3 event(s) the participant is permitted to resume study drug, but has an additional event (AST and/or ALT) at a Grade 3 level, the IoR must permanently discontinue the study drug, offer symptomatic treatment (if appropriate), and order any clinically relevant laboratory analyses (per judgment of the IoR).

> 10.0 x ULN (Grade 4)	Permanently discontinue study drug	Study drug should be permanently discontinued for any Grade 4 AST or ALT and the CMC should be immediately notified. Participants should have AST/ALT re-checked as soon as possible (at most within 1 week of the receipt of the results). Participants should then be followed weekly until levels are $\leq 2 \times$ ULN transaminase unless indicated by the CMC.
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14.2.3 EKGs: Measurement of QTcF

Participants with a QTcF > 500 ms and/or an increase in QTcF from baseline of > 60 ms must have a confirmatory measurement, preferably within 48 hours after the EKG results have become available.

If the QTcF > 500 ms and/or the increase in QTcF from baseline of > 60 ms are confirmed, intake of study product (oral or injectable) must be permanently discontinued. Participants will continue to be followed.

CONDITION AND SEVERITY	STUDY DRUG USE	FOLLOW-UP AND MANAGEMENT
Prolonged QTcF		
Asymptomatic, QTcF interval 0.45 – 0.47 sec OR Increase interval < 0.03 sec above baseline (Grade 1)	Continue	None required.
Asymptomatic, QTcF interval 0.48 – 0.49 sec OR Increase in interval 0.03 – 0.05 sec above baseline (Grade 2)	Temporarily discontinue	Temporarily discontinue and consult with CMC if deemed to be study drug related. Repeat EKG in 48 hours.
Asymptomatic, QTcF interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline (Grade 3)	Permanently discontinue	Repeat EKG within 48 hours. If prolongation confirmed, stop all study products permanently. Treat symptoms appropriately. Notify CMC.
Life-threatening consequences, e.g. Torsade de pointes or other associated serious ventricular dysrhythmia (Grade 4)	Permanently discontinue	If detection of 4+ QTcF at any visit, study drug should be permanently discontinued. Intervene urgently as appropriate. Refer for ongoing management after emergency treatment. Notify CMC

14.2.4 Acute Systemic Allergic Reaction

Participants should be advised to contact the research site immediately if there is any acute systemic allergic reaction.

CONDITION AND SEVERITY	STUDY DRUG USE	FOLLOW-UP AND MANAGEMENT
Acute Systemic Allergic Reaction		
Localized urticaria (wheals) with no medical intervention indicated (Grade 1)	Continue	May treat symptomatically. Review within 48 hours if thought to be study drug related and advise participant to return if any worsening.
Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated (Grade 2)	Continue or interrupt study drug if deemed unrelated to study medication at discretion of IoR and consult with CMC. If deemed to be study drug related temporarily withhold study product and consult with CMC.	Treat symptomatically as required. May require temporary withdrawal of study product. Inquire for possible alternative causative agents. Drug can be recommenced after consultation with CMC. Treat symptoms. Blood should be drawn for AST, ALT, and a CBC (including hemoglobin, hematocrit, RBC, WBC, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelet count).
Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm (Grade 3)	Permanently discontinue	If detection of 3+ systemic reaction at any visit, study drug should be permanently discontinued. Inquire about other alternative causative agents. Treat symptoms appropriately. Blood should be drawn for AST, ALT, and a CBC (including hemoglobin, hematocrit, RBC, WBC, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelet count). Notify CMC.
Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema (Grade 4)	Permanently discontinue	If detection of 4+ systemic reaction at any visit, study drug should be permanently discontinued. Intervene urgently as appropriate. Refer for ongoing management after emergency treatment. Notify CMC. Blood should be drawn for AST, ALT, and a CBC (including hemoglobin, hematocrit, RBC, WBC, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelet count).

14.2.5 Injection Site Reactions

CONDITION AND SEVERITY	STUDY DRUG USE	FOLLOW-UP AND MANAGEMENT
Injection site reactions		
Pain/tenderness causing no or minimal limitation (Grade 1)	Continue	May treat symptomatically.
Pain/tenderness causing greater than minimal interference with usual social & functional activities (Grade 2)	Continue in consultation with CMC	Treat symptomatically as required.
Pain/tenderness causing inability to perform usual social & functional activities (Grade 3)	Continue or interrupt study drug at discretion of IoR and consult with CMC	Treat symptomatically as required. May require temporary withdrawal of study product. Drug can be recommenced after consultation with CMC. Treat symptoms.
Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than emergency room visit) indicated for management of pain/tenderness (Grade 4)	Permanently discontinue	If detection of 4+ IS reaction at any visit, study drug should be permanently discontinued. Intervene urgently as appropriate. Refer for ongoing management after emergency treatment. Notify CMC.
Erythema OR Induration of 5x5 cm – 9x9 cm (or 25 cm ² – 81cm ²) (Grade 1)	Continue	May treat symptomatically.
Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm ²) (Grade 2)	Continue in consultation with CMC	Treat symptomatically as required.
Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage (Grade 3)	Interrupt study drug at discretion of IoR and consult with CMC	Treat symptomatically and refer for further surgical management as required.
Necrosis involving dermis and deeper tissue (Grade 4)	Discontinue	Treat symptomatically and refer for further surgical management as required.

14.2.6 Rash

In case of rash, visits and assessments should be performed as described in detail in the SSP.

Participants must be informed that they should contact their study site as soon as possible after onset of a rash. The participant should be evaluated as soon as possible (unscheduled visit). In addition, the participant should be advised to contact the IoR immediately if there is any worsening of the rash, including occurrence or worsening of any systemic signs or symptoms of mucosal involvement.

The participant may be treated symptomatically until the rash resolves. If the rash is considered to be most likely due to concomitant illness or non-study medication, standard management, including discontinuation of the likely causative agent, should be undertaken, and the continuation of the participant in the study should be discussed with the CMC.

CONDITION AND SEVERITY	STUDY DRUG USE	FOLLOW-UP AND MANAGEMENT
Skin rash		
Localized macular rash (Grade 1)	Continue unless management states otherwise	<p>A finding of 1+ skin rash should be treated symptomatically. Inquiries should be made about other possible causative agents or conditions. Blood should be drawn for AST, ALT, and a CBC (including hemoglobin, hematocrit, RBC, WBC, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelet count).</p> <p>Additional safety blood samples are to be taken <u>if</u> the participant's AST/ALT on Day zero <u>and/or</u> Day one of rash > two x baseline value, and/or ≥ five x ULN and/or in case of rash progression.</p> <p>Participant should be examined for evidence of systemic involvement: fever, malaise or mucosal involvement. If so, drug should be held and CMC consulted.</p> <p>Review within 48 hours and advise participant to return urgently if worsening of rash.</p>

<p>Diffuse macular, maculopapular, or morbilliform rash OR Target lesions</p> <p>(Grade 2)</p>	<p>Temporarily hold study drug as per follow-up and management</p>	<p>A finding of 2+ skin rash should be treated symptomatically. Inquiries should be made about other possible causative agents or conditions. Blood should be drawn for AST, ALT, and a CBC (including hemoglobin, hematocrit, RBC, WBC, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelet count).</p> <p>Additional safety blood samples are to be taken <u>if</u> the participant's AST/ALT on Day zero <u>and/or</u> Day one of rash > two x baseline value, and/or ≥ five x ULN and/or in case of rash progression.</p> <p>Participant should be examined for evidence of systemic involvement: fever, malaise or mucosal involvement. If any present, drug should be held and CMC consulted.</p> <p>Review within 48 hours and advise participant to return urgently if worsening of rash.</p>
<p>Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site</p> <p>(Grade 3)</p>	<p>Permanently discontinue</p>	<p>If detection of 3+ or greater skin rash at any visit, study drug should be permanently discontinued regardless of serum or plasma LFTs and CMC contacted immediately. A finding of 3+ skin rash should be treated symptomatically. Inquiries should be made about other possible causative agents or conditions. Blood should be drawn for AST, ALT, and a CBC (including hemoglobin, hematocrit, RBC, WBC, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelet count).</p> <p>Additional safety blood samples are to be taken <u>if</u> the participant's AST/ALT on Day zero <u>and/or</u> Day one of rash > two x baseline value, and/or ≥ five x ULN and/or in case of rash progression. Weekly follow-up visits are required (or more frequently at the IoR's discretion) as long as Grade 3-4 rash is present.</p> <p>Participant should be examined for evidence of systemic involvement: fever, malaise or mucosal involvement.</p> <p>A dermatologic referral should be considered.</p>

Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN) (Grade 4)	Permanently discontinue	If detection of 4+ or greater skin rash at any visit, study drug should be permanently discontinued regardless of serum or plasma LFTs and CMC notified immediately. A finding of 4+ skin rash is an emergency and must trigger a specialist referral or referral to an emergency center for possible admission and acute management. Inquiries should be made about other possible causative agents or conditions. Blood should be drawn for AST, ALT, and a CBC (including hemoglobin, hematocrit, RBC, WBC, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelet count).
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14.2.7 Depression/Suicidality

CONDITION AND SEVERITY	STUDY DRUG USE	FOLLOW-UP AND MANAGEMENT
Depression/Suicidality		
Depression or mood alteration causing no or minimal interference with usual social & functional activities (Grade 1)	Continue	May treat symptomatically.
Depression or mood alteration causing greater than minimal interference with usual social & functional activities (Grade 2)	Continue or interrupt study drug at discretion of IoR and consult with CMC depending on relatedness to study product	Treat symptomatically as required. May require temporary withdrawal of study product. Inquire for possible alternative causative agents. Drug can be recommenced after consultation with CMC. Treat symptoms.
Depression or mood alteration causing inability to perform usual social & functional activities (Grade 3)	Permanently discontinue	If detection of 3+ depression at any visit, study drug should be permanently discontinued. Treat symptoms appropriately. Notify CMC.
Behavior potentially harmful to self or others (e.g., suicidal and homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions (Grade 4)	Permanently discontinue	If detection of 4+ depression or suicidality at any visit, study drug should be permanently discontinued. Intervene urgently as appropriate. Refer for ongoing management after emergency treatment. Notify CMC.

15.0 APPENDIX III: SAMPLE INFORMED CONSENT FORMS

SAMPLE SCREENING AND ENROLLMENT INFORMED CONSENT FORM

Phase II Safety and Acceptability of an Investigational Injectable Product, TMC278 LA, for PrEP (HPTN 076)

**Final Version 2.0
1 October 2014
DAIDS Document ID: 11944**

Study Implementers:

Emavundleni Desmond Tutu HIV Centre, Cape Town, South Africa;
Spilhaus Clinical Research Site, Harare, Zimbabwe;
Division of Infectious Diseases, UMDNJ-New Jersey Medical School, Newark, NJ, USA;
Bronx Prevention Center, Columbia University, Bronx, NY, USA

Study Sponsors: NIH, Division of AIDS (DAIDS), US National Institute of Allergy and Infectious Diseases (NIAID). Study drug is provided by Janssen Pharmaceuticals.

IND Holder: PATH Drug Solutions (PDS)

PRINCIPAL INVESTIGATOR: [Insert Name]

PHONE: [Insert Number]

Introduction

You are being asked to take part in an HIV research study. HIV is the virus that causes AIDS. The goal of the research is to find out two things: 1) if a new drug that may prevent HIV infection is safe, and 2) whether women are willing to receive injections (shots) of the new drug. The study will also ask women how they feel about getting the shots.

This study is being offered to about 132 women in both Africa and the United States. Whether you join the study or not is up to you. If you choose to join the study, you may stop taking part at any time.

There may be no direct benefits for you if you participate in this study. There also may be some risks with taking part in the study. Before you can make an informed decision about whether to join this study, you should understand the possible risks and potential benefits of being in this study. The process of explaining the risks and benefits is called informed consent. This document describes what will happen during the study and provides you with detailed information about this research study. This form might have some words in it that are not familiar to you. Please ask us to explain anything that you do not understand before you sign this form. If you tell us that you understand the study and have decided that you want to join it, you will be asked to read, sign, and date this form. You will also be offered a copy of this form to keep.

Study Purpose

The purpose of this study is to find out whether a new drug is safe. The drug is being developed for both the treatment and prevention of HIV. The drug being used in this study has not been approved for use by the US Food and Drug Administration (FDA), which is the part of the US government that approves medicines. The study drug is called “long acting rilpivirine” or

“TMC278 LA.” The regular form of rilpivirine is not long acting and is an FDA approved drug that is used in people who have an HIV infection. Both rilpivirine and the long acting rilpivirine are a type of drug called an antiretroviral drug. Antiretroviral drugs usually come in the form of pills, but newer kinds are becoming available as an injection, or a shot.

In this study, we want to find out whether the injection form of rilpivirine (the long acting form) is safe, as well as to see how people who get the injection form of rilpivirine respond to it (meaning, does it make you feel sick). Another reason we are doing this study is to find out whether people in the study are willing to receive the injections (shots) of the long acting rilpivirine and how they feel about it. The injections are given as 2 shots in your buttocks 6 times during the study (a total of 12 shots). The injections are NOT HIV vaccinations.

In addition to the injections, rilpivirine pills are used in the study. You will be given rilpivirine pills to make sure that you do not have a bad reaction to the drug before you are given an injection. The injection form of rilpivirine (the long acting rilpivirine) is active in the body for weeks. It is important that you take the rilpivirine pills given to you because once an injection of the long acting drug is given, it is impossible to get the drug back out of your body. The long acting rilpivirine used in the injection has been given to about 150 men and women so far, and has not caused many side effects.

You are being asked to participate in this study because you are at low risk of getting HIV. We do not know whether the drug being used in this study will prevent a person from getting HIV, and that is why we need volunteers who have a low risk of getting HIV.

Even though you are at low risk, we will remind you every time we see you for your study visits that one of the best things that you can do to protect yourself against getting HIV during sex is to use a condom every time you have sex.

We will also ask you to let us know if your risk for getting HIV has changed while you are in the study, and also to let us know whether you think that you may have been exposed to HIV through sex or intravenous drugs.

If you think you are at risk for getting HIV, you should not participate in this study.

Study Groups

If you decide to take part in the study, you will be placed in 1 of 2 groups:

- One group will be given pills and injections that have rilpivirine in them. There will be 88 women in this group.
- One group will be given pills and injections that do not have rilpivirine in them. These pills and injections are called placebos. The placebo forms of the drug typically look like the active or “real” drug, but they do not have the drug or any other medicine in them. There will be 44 women in this group.

The study group that you will be in is chosen randomly, like flipping a coin. You cannot choose your group and the study staff cannot choose your group. Each group is very important to the study.

Two out of three women (or 66%) will be in the group that is given rilpivirine pills and long acting rilpivirine injections. One out of three women (or 33%) will be in the group that will not receive any rilpivirine. *[Sites may insert another way to describe the 2:1 randomization that may be more appropriate to the local population].*

Neither the study staff nor you will know which group you are in until a planned time during the study. When that time is reached, we will let everyone know which group they are in. Your participation in the study may have ended by the time, but we will contact you to let you know.

If you are still in the study when we let everyone know which group they are in, that will be the time that your participation in the study will end. Even if you are in the group that did not receive rilpivirine, your participation in that group is very important because it gives us a chance to compare what happens to you with a person that did get the drug.

What happens if you do not want to take part in the study?

Before you learn more about the study it is important that you know the following:

- You do not have to join this study.
- You can stop taking part in the study at any time.
- During the study, you may be told of important new information about the study that may affect your original decision to join. It will be up to you to decide if you want to continue in the study. If you decide to stay in the study, we may ask you to sign an updated informed consent form.
- If you or your doctor decides that you should withdraw from the study we may ask you to come in for a final visit.
- Whether or not you take part in this study, you will still continue to receive the same services you get at [insert clinic].

What will happen if you do want to join this study?

If you have been screened and are eligible, and if you decide to join the study, you will need to agree to:

- complete 18 more study visits at this clinic over the course of a year and a half (18 months),
- get tested for an HIV infection, the hepatitis B infection (HBV), hepatitis C infection (HCV), and other sexually transmitted infections by us,
- have a routine heart test called an “EKG,”
- receive the test results,
- take a pill by mouth daily for the first 4 weeks,
- receive 2 injections in your buttocks 8 weeks apart; injections will be given at 6 different times in the study for a total of 12 injections,
- record any symptoms you may have for 7 days after you receive injections,
- tell us what you think about the injections,
- give us urine and blood samples,
- give us swabs that were wiped on the vagina, [Optional: Only for sites that perform testing on swabs, urine may be used at some sites.]
- allow us to collect cervicovaginal and rectal fluid (at one visit only),
- agree to use birth control during the study and also 1 month afterward, unless you have had surgery which prevents you from getting pregnant,
- not participate in other HIV research studies during while you are in this study.

What happens during the Screening Visit?

This study visit is called the Screening visit. The visit will take about XX minutes and will help us to know if you are eligible to join the study. During this visit, you will be asked questions about your health, sexual practices, and personal life to see if you are eligible to participate. We

will ask your name and contact information so that we can keep in touch with you during the study.

We will give you a full physical exam and ask about your medical history. We will also do the tests described below.

- We will draw ~XX mL of blood (about X tablespoons). Your blood will be tested for an HIV infection. We will counsel you about HIV infection and risks you may be taking. If the tests indicate that you may be infected with HIV, you may be asked to come back to the clinic again for additional testing. Some of the blood will be stored to check that test results from the study are correct and to perform other tests related to HIV prevention.
- We will use the blood sample to test you for a liver infection, hepatitis B (HBV) and hepatitis C virus (HCV).
- We will ask you for a urine sample. We will test your urine to see if you are pregnant.
- We will ask for a vaginal swab to test for sexually transmitted infections. Alternatively we may be able to use urine for this testing.
- Your samples (blood and urine) will be tested to assess you for any sexually transmitted infections. Your blood and urine will be tested to assess your overall health, and to see if your liver and kidneys are working normally.
- An electrocardiogram (EKG) will also be performed. An EKG is a recording of the heart's electrical activity. This is a routine test that involves attaching sticky pads with small wires to your arms, legs and chest to read the electrical impulses of your heart. This test is considered a standard medical test to assess heart function.

You will be offered condoms and lubrication.

After all of the screening test results are available, the study staff will let you know if you are eligible. If you are eligible and decide to join the study, you will need to come back for 18 more study visits over the next 18 months.

Visit #1: Enrollment visit: The first study visit is called the Enrollment visit. The visit will take about XX minutes. Study staff will review your contact information so that we can keep in touch with you during the study. We will ask some questions to help us understand your opinions about taking pills and getting injections to prevent HIV infection.

We will assign you to one of the study groups. We will give you pills to take home with you and we will explain how to take the pills. We will ask you to take a pill today at the clinic in front of a staff member. We will provide a meal to eat when you take the pill, because that is how the drug should be taken.

We will ask you if there have been any changes in your health since the last visit. If you are having problems, we may do a medical examination. We will also do the tests described below.

- We will draw ~XX mL of blood (about X tablespoons). Your blood will be tested for

an HIV infection. We will counsel you about HIV infection and risks you may be taking. If the tests indicate that you may be infected with HIV, you may be asked to come back to the clinic again for additional testing. Some of the blood will be stored to check that test results from the study are correct and to perform other tests related to HIV prevention.

- Some blood will be used to test for rilpivirine before we give you study drug. We will also study your DNA to learn more about how the study drug is processed in your body. In addition, your blood samples may be tested for the presence of other medications that might impact how the study drug is processed in your body.
- We will ask you for a urine sample. We will test your urine to see if you are pregnant.
- Your blood and urine will be tested to assess your overall health, and to see if your liver and kidneys are working normally.

You will be offered condoms and lubrication.

Visits #2-6: First 2 Weeks: We will ask you to come to the clinic and take the study pill in front of a staff member. We will provide a meal to eat when you take the pill, because that is how the drug should be taken. By having you take a pill in front of us, we can be sure you have taken the pill several times before you receive an injection. It is very important that you take the pills to make sure that you do not have a bad reaction to rilpivirine before you are given an injection of the long acting rilpivirine at Week 4. The injection form of rilpivirine is active in the body for weeks and once an injection of the drug is given to you, it is impossible to get the drug back out of your body.

During some of these visits, we will count the number of pills that you have taken and we will talk to you to see if you are having any difficulty remembering to take the pills. During the visit at Week 2, we will check your skin to see if the study pill caused you to have a rash. We will also review your contact information and provide HIV risk reduction counseling. These visits will take about XX minutes.

During two of these visits, we will ask you if there have been any changes in your health since the last visit. If you are having problems, we may do a medical examination. To make sure that you are not having a bad reaction to the study pill, we will do the tests described below.

- We will draw ~XX mL of blood (about X tablespoons). Your blood will be tested for an HIV infection. We will counsel you about HIV infection and risks you may be taking. If the tests indicate that you may be infected with HIV, you may be asked to come back to the clinic again for additional testing. Some of the blood will be stored to check that test results from the study are correct and to perform other tests related to HIV prevention.
- Some blood will be used to test for rilpivirine to help us learn more about how your body processes the study drug. Your blood samples may also be tested for the presence of other medications that might impact how the study drug is processed in your body.
- We will ask you for a urine sample. We will test your urine to see if you are pregnant.

- Your blood and urine will be tested to assess your overall health, and to see if your liver and kidneys are working normally.

You will be offered condoms and lubrication.

Visit #7: Week 4: This visit will take about XX minutes. Study staff will review your contact information so that we can keep in touch with you during the study. We will ask some questions to help us understand your opinions about taking pills and getting injections to prevent HIV infection. We will count the number of pills that you have taken and we will talk to you to see if you are having any difficulty remembering to take the pills.

We will ask you if there have been any changes in your health since the last visit. If you are having problems, we may do a medical examination. We will also do the tests described below.

- We will draw ~XX mL of blood (about X tablespoons). Your blood will be tested for an HIV infection. We will counsel you about HIV infection and risks you may be taking. If the tests indicate that you may be infected with HIV, you may be asked to come back to the clinic again for additional testing. Some of the blood will be stored to check that test results from the study are correct and to perform other tests related to HIV prevention.
- Some blood will be used to test for rilpivirine to help us learn more about how your body processes the study drug. Your blood samples may also be tested for the presence of other medications that might impact how the study drug is processed in your body.
- We will ask you for a urine sample. We will test your urine to see if you are pregnant.
- Your blood and urine will be tested to assess you for your overall health and to see if your liver and kidneys are working normally.
- An electrocardiogram (EKG) will also be performed. An EKG is a recording of the heart's electrical activity. This is a routine test that involves attaching sticky pads with small wires to your arms, legs and chest to read the electrical impulses of your heart. This test is considered a standard medical test to assess heart function.
- We will give you the first set of injections. You will receive 2 injections, 1 injection in each buttock. Each injection will have about ½ teaspoon (2 mLs) of fluid. We will also talk to you about any side effects that you might experience after receiving the injections.

Each time you have injections, we will give you something for you to take home with you to record any symptoms you may have for 7 days after the injections. You will need to bring it back with you to your next clinic visit so that we can review it with you.

You will be offered condoms and lubrication.

Visits #8, 9 & 11: Weeks 6, 8, and 14: These visits will take about XX minutes. Study staff will review your contact information so that we can keep in touch with you during the study.

We will ask you if there have been any changes in your health since the last visit. If you are having problems, we may do a medical examination. We will examine your skin where you received the injections at Week 4 and at Week 12. If you were given something at your last visit to take home with you to record any symptoms after injections, we will review that with you. We will also do the tests described below.

- We will draw ~XX mL of blood (about X tablespoons). Your blood will be tested for an HIV infection. We will counsel you about HIV infection and risks you may be taking. If the tests indicate that you may be infected with HIV, you may be asked to come back to the clinic again for additional testing. Some of the blood will be stored to check that test results from the study are correct and to perform other tests related to HIV prevention.
- Some blood will be used to test for rilpivirine to help us learn more about how your body processes the study drug. Your blood samples may also be tested for the presence of other medications that might impact how the study drug is processed in your body.
- We will ask you for a urine sample. We will test your urine to see if you are pregnant.
- Your blood and urine will be tested to assess you for your overall health and to see if your liver and kidneys are working normally.

You will be offered condoms and lubrication.

Visits # 10, 12-15: Weeks 12, 20, 28, 36 and 44: These visits will take about XX minutes. Study staff will review your contact information so that we can keep in touch with you during the study.

We will ask you if there have been any changes in your health since the last visit. If you are having problems, we may do a medical examination. We will examine your skin where you received the last injections. We will also do the tests described below.

- We will draw ~XX mL of blood (about X tablespoons). Your blood will be tested for an HIV infection. We will counsel you about HIV infection and risks you may be taking. If the tests indicate that you may be infected with HIV, you may be asked to come back to the clinic again for additional testing. Some of the blood will be stored to check that test results from the study are correct and to perform other tests related to HIV prevention.
- Some blood will be used to test for rilpivirine to help us learn more about how your body processes the study drug. Your blood samples may also be tested for the presence of other medications that might impact how the study drug is processed in your body.
- We will ask you for a urine sample. We will test your urine to see if you are pregnant.
- Your blood and urine will be tested to assess you for your overall health and to see if your liver and kidneys are working normally.

- An electrocardiogram (EKG) will also be performed. An EKG is a recording of the heart's electrical activity. This is a routine test that involves attaching sticky pads with small wires to your arms, legs and chest to read the electrical impulses of your heart. This test is considered a standard medical test to assess heart function.
- We will give you 2 injections, 1 injection in each buttock. Each injection will have about ½ teaspoon (2 mLs) of fluid. We will also talk to you about any side effects that you might experience after receiving the injections.
- During the visit at Weeks 28 and 44, we will ask some questions to help us understand your opinions about taking pills and getting injections to prevent HIV infection.
- **PLEASE NOTE: At only one of the study visits at either Week 36 or Week 44 (not both), we will collect fluid from your vagina and fluid from your rectum to see how the injectable study drug is processed in these fluids.**

Each time you have injections, we will give you something for you to take home with you to record any symptoms you may have for 7 days after the injections. You will need to bring it back with you to your next clinic visit so that we can review it with you.

You will be offered condoms and lubrication.

Visits #16 - 18: Weeks 52, 64 and 76: These visits will take about XX minutes. Study staff will review your contact information so that we can keep in touch with you during the study.

We will ask you if there have been any changes in your health since the last visit. If you are having problems, we may do a medical examination. We will also do the tests described below.

- We will draw ~XX mL of blood (about X tablespoons). Your blood will be tested for an HIV infection. We will counsel you about HIV infection and risks you may be taking. If the tests indicate that you may be infected with HIV, you may be asked to come back to the clinic again for additional testing. Some of the blood will be stored to check that test results from the study are correct and to perform other tests related to HIV prevention.
- Some blood will be used to test for rilpivirine to help us learn more about how your body processes the study drug. Your blood samples may also be tested for the presence of other medications that might impact how the study drug is processed in your body.
- We will ask you for a urine sample. We will test your urine to see if you are pregnant.
- Your blood and urine will be tested to assess you for your overall health and to see if your liver and kidneys are working normally.

At the Week 52 visit only, we will examine your skin where you received the last injections. We will review the memory aid we sent home with you after the injections at Week 44.

You will be offered condoms and lubrication.

What will happen if you have a positive test result?

[Sites to include/amend the following if applicable:] Please understand that [Local/state/national] regulations require study staff to report the names of people who test positive for [HIV and other infections] passed during sex to the [local health authority]. Outreach workers from the [health authority] may then contact you about informing your partners, since they also should be tested. If you do not want to inform your partners yourself, the outreach workers will contact them, according to the confidentiality guidelines of the [health authority].

What if your blood test shows that you may have HIV?

Should a test result indicate that you may have been infected with HIV before you are enrolled into the study, we will need to do confirmatory testing and you will need to return to the clinic for this testing. If the confirmatory tests show that you have an HIV infection, you will not be able to join the study and we will refer you for HIV treatment and care.

Should a test result indicate that you may have become infected with HIV after you are enrolled into the study, we will need to do confirmatory testing and you will need to return to the clinic for this testing. If the confirmatory tests show that you have an HIV infection, we will do lab tests to see how well your body can fight off infections, we will measure the amount of HIV virus in your blood, we will store blood, and we will ship stored samples to designated laboratories in the United States during and after the study to see if the HIV in your blood is resistant to drugs used to treat HIV infection. The laboratories in the United States may also do other HIV-related tests to help us understand the type of virus you were infected with and your body's immune response to the HIV virus. To assist with your clinical care during the study, we may also order tests to see if the HIV in your blood is resistant to drugs used to treat HIV infection.

What if a test result shows that you have a hepatitis infection?

If a test results shows that you have a hepatitis B or hepatitis C infection, we will refer you for appropriate medical care and treatment.

What if a test result shows that you have a sexually transmitted infection?

If a test result shows that you have a sexually transmitted infection, we will offer you care here at this clinic.

What if the EKG shows an abnormality?

If an EKG performed indicates that you might have unusual heart activity, we will refer you to a medical clinic for care and treatment.

Sample Storage

Each time blood is taken during a study visit, we will store a sample. Stored samples will be sent to designated laboratories in the United States for the following reasons:

- to confirm that study test results are correct,
- to test for rilpivirine and to study your DNA to help us learn more about how your body processes the study drug,
- to test for the presence of other medications that might impact how the study drug is processed in your body.

Cervicovaginal and rectal fluid samples will also be sent to designated laboratories in the United States to test for rilpivirine and to study how the drug is processed in your body.

Some blood samples may be shipped to designated laboratories in the United States for STI testing. Some sites may be asked to store other types of samples (urine or swabs) if the site is

not able to perform the required STI testing; those samples would be analyzed at the laboratories in the United States.

If test results indicate that you become infected with HIV after you are enrolled in the study, we will ship blood samples to designated laboratories in the United States for additional testing described above in the “What if your blood test shows that you may have HIV?” section.

Leftover Samples

There may be some leftover samples of blood [depending on STI method used, site may need to add “swabs” here] after all of the study testing has been completed. We would like to use these samples for future research studies related to HIV treatment and prevention. Before your leftover samples could be used we would have to ask for approval from the leadership group of the HIV Prevention Trials Network (HPTN).

If you do not agree to have your leftover samples stored, you can still be in this study. If you agree to store your samples but change your mind later, you can contact study staff. We will then destroy your samples.

If you agree to this use of your samples, we will ask you to initial the end of this form. Samples will be sent to designated laboratories in the United States for further testing. Your leftover samples will be stored indefinitely [insert local guidelines]. Any future use or the ability to store your samples longer needs to be reviewed and approved by the NIH and local authorities. If these studies involve other laboratories, we will need approval from your local authorities to store or transfer them elsewhere. Your leftover samples will not be sold or used for commercial reasons.

What are the possible risks or discomforts?

Sensitive questions

The questions we will ask you about your sexual behavior may make you feel uneasy. However, you do not have to answer any question that you do not want to and you can stop answering the questions at any time.

Blood samples

Taking blood samples may cause some pain, bruise your arm, or make you feel lightheaded. In rare cases, you may faint. There is also a slight chance of infection when blood is drawn.

HIV testing stress

You may be nervous while you are waiting for your HIV test result. If the tests show that you have HIV, you may worry about your health and future. You will receive counseling before and after the test to help address your concerns.

Confidentiality

To keep your information private, your samples will be labeled with a code that can only be traced back to your study clinic. Your name, where you live, and other personal information will be protected by the study clinic. The results of any tests done on these samples will not be included in your health records. Every effort will be made to keep your personal information confidential, but we cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

Social Impact

Although every effort will be made to protect your privacy and confidentiality, it is possible that your involvement in the study could become known by others in your community. They might think you have HIV or that you are at high risk of becoming infected with HIV, and they may

treat you unfairly.

Cervicovaginal and Rectal Fluid Collection

You might feel discomfort or embarrassment during the fluid sample collection process.

Possible risks to taking the study pill and injection

- **General side effects**

Some people experience side effects when they take a medicine. It is possible that you could have a headache, feel tired, or have a dry mouth. It is also possible that you could feel dizzy or that your sleeping could change. Some people have trouble going to sleep when taking the study medicine, some people feel more sleepy than usual, and some people have unusual dreams.

It is also possible that you could experience a side effect to the drug that is not yet known.

- **Digestive problems**

It is possible that you could have abdominal pain, feel like vomiting or vomit. It is also possible that you will feel less hungry than usual.

- **Liver problems**

It is possible that the study drug could harm your liver. We will use blood tests to monitor the function of your liver at the beginning of the study and then throughout the study. You will be told by study staff if we detect any harmful changes in your liver, and we may decide to stop giving you study drug.

- **Rash**

It is possible that you could develop a rash. We will check your skin for a rash. You should contact us right away if you do develop a rash.

- **Depression**

It is possible that you could start to feel sad or anxious while taking the study pill or after the study drug injection. It is also possible that you might have feelings of hurting yourself. You should contact us right away if you experience any of these symptoms.

- **Changes in body fat**

It is possible that you may have changes in where your body fat is. You may lose some body fat from your legs, arms, and face and you could gain fat in your waist, breasts, neck, and back.

- **Allergic reaction**

It is possible that you may be allergic to the drug in the pill or injection. Symptoms of an allergy include itching all over, hives (pink rash that itches), sneezing, wheezing (whistling sound made in the lungs while breathing), nausea, vomiting, and diarrhea. You should contact us right away if you do have these symptoms.

- **Injection site reaction**

It is possible that when you get the injections, the area around the injection could be sore or tender. It is also possible that the skin could swell, become red or change in color, bruise, or feel warm. You should contact us right away if you do have these symptoms.

- **Resistance to the study drug**

It is possible that by taking the study drug you could become “resistant” to it if you become infected with the HIV virus while taking it. This means that the study drug would not be able to control the HIV virus in your body. You would need to take different medicines to control the HIV virus.

We will talk with you about this problem and help you understand how to protect yourself against becoming resistant. It is not known how long the injected study drug could stay in your body based on current information so you will need to be especially careful to protect yourself from becoming infected with HIV during the study, and for a period of time after the study.

If you do become infected with HIV during the study, you will be offered medication for the period of one year to control the HIV virus (called ART) while the long acting rilpivirine is still in your body. By giving you ART to control the HIV virus, we will reduce the chance of resistance to the long acting rilpivirine injection. At the end of the year, if you wish to keep taking ART we will transfer you to a local HIV clinic where you will receive HIV care and ART.

If you need to stop taking the study pills or receiving injections during the study for any reason, we would still like you to stay in the study and continue to come to appointments.

What are the potential benefits?

We will check to see if you have HIV infection, hepatitis B or C infection, or other sexually transmitted infections. The counseling you get during this study may help you to avoid HIV, hepatitis, and other sexually-transmitted infections. If tests show that you have HIV, hepatitis, or a sexually transmitted infection counseling we provide may help you to learn how to better care for yourself and avoid passing an infection to your sexual partners.

We will also do medical exams and lab tests to check the general health of your liver, kidneys, and heart. You will be offered condoms and lubricant free of charge.

What are the alternatives to participating in this study?

You do not have to join this study.

[Sites to amend as applicable] There may be other studies going on at this study clinic or in the community for which you may be eligible. If you wish, we will tell you about other studies that we know about. There may also be other places where you can go for HIV counseling and testing. We will tell you about those places if you wish.

How will your privacy be protected?

All the information you give us as part of this study will be kept private. All your laboratory test results will also be kept private. You will get a unique study identification number that will be used instead of your name on your documents. However, at every study visit we will ask you to identify yourself. This is to make sure that it is you who provides samples and information to us. Also we want to make sure that no other person than you can get your confidential laboratory test results. Only the study staff will be able to see records that identify you by name. This information will not be shared with others. All records will be stored in locked files at the study clinic. Results of your laboratory tests will be made available only to you when you visit the clinic. Your name will never be used in any publication or presentation about the study.

Your records may be reviewed by the sponsor of the study, the US National Institutes of Health (NIH) and their representatives, FDA and other government and regulatory authorities, authorized representatives of PDS and/or its contractors, **[insert name of site]** IRB/EC, study staff, study monitors and [insert applicable local regulatory authorities].

We cannot guarantee absolute confidentiality. [For US sites: In addition to the efforts made by the study staff to help keep your personal information confidential, we have obtained a Certificate of Confidentiality from the U.S. Federal Government. This certificate protects researchers from being forced to tell people who are not connected with this study, such as the court system, about your participation.

Also, the Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, we will tell the proper authorities.]

A description of this study will be available on www.ClinicalTrials.gov, as required by US law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

How will study staff keep in contact with you during the study?

You will be asked to provide your address and phone number(s). The staff will ask you for names of people who will always know how to find you and places where you can be found. It is possible that the staff may visit you at your house or contact one of the people on your contact list if you are not able to attend your visits or if the staff members have important information for you. If we talk to people on this list, we will not tell them why we are trying to reach you. If you are not willing to give us this information, you should not agree to be in this study.

Reasons why you may be withdrawn from the study without your consent

Your participation in the study may be ended early without your consent for the following reasons:

- The research study is stopped or canceled.
- The study staff feels that staying in the study would be harmful to you.
- The study investigators identify other reasons that they believe would prevent you from continuing in the study.
- Finally, the study can be stopped by local authorities, such as the ethical review committee, or by other agencies, such as the study sponsor or other oversight agencies.
- During the study, you may be told of important new information about the study that may affect your safety. For example, if the study shows that you taking part in it may be bad for your health, we will tell you. It will be up to you to decide if you want to continue in the study. If you decide to stay in the study, we may ask you to sign an updated informed consent form. You will also be told when the results of the study may be available, and how to learn about them.
- If you have any major health problems during the study, the doctor may require that you stop taking study drug for your own safety.
- If you or your doctor decides that you should withdraw from the study we may ask you to come in for a final visit.

How will the study drug affect pregnancy or breastfeeding?

Women who join the study must agree to use effective contraception during the study and 1 month after the study unless they have had surgery which prevents them from getting pregnant. Women who join will also must have pregnancy tests and answer questions about your current family planning method at the Screening Visit, and at other visits while in the study. Effective contraception includes hormonal methods (such as the birth control pill or shot), intrauterine contraceptive device (IUD), and sterilization. Condoms are the only method which also protect you against HIV infection and should be used from start to finish every time you have sex even if you are using another contraceptive method.

If you are pregnant or breastfeeding, you cannot join this study. If you become pregnant during the study, or within 28 days after completing the study, you should notify the study personnel right away for your safety. If you become pregnant during the study, you will stop receiving pills or shots right away. The study staff will refer you to available sources of medical care and other services for you or your baby. The study does not pay for this care.

Please tell your doctor during your pregnancy about your study participation. Your study doctor will ask that you, or your doctor, provide updates on the progress of your pregnancy and its outcome. The study doctor will make this information available to the study sponsor for safety monitoring follow-up.

We do not know if the study drug injections have any effect on babies whose mothers take it during pregnancy or when breastfeeding. Because of this, **women who are pregnant or breastfeeding cannot participate in this study.**

What happens if you are injured by this research?

Taking part in this study may put you at risk for personal injury. You may develop side effects from the study drug. If such side effects happen, study staff will assist you in getting medical care. *[Sites to specify institutional policy:]* It is unlikely that you will be injured as a result of taking part in this study. If you are injured, the *[institution]* will give you the treatment needed for your injuries. You *[will/will not]* have to pay for this treatment. You will be told where you can get additional treatment for your injuries. There is no program to pay money or give other forms of compensation for such injuries through the United States NIH. You do not give up any legal rights by signing this consent form.

Who can you contact if you have any questions?

We are happy to answer any questions that you may have. It may be that you have questions about your rights as a study participant or that you think you have been injured because you were in this study. In this case you can contact *[insert name of the investigator or other study staff]* at *[insert telephone number and physical address]*.

If you have any questions or concerns about whether you should join this study, or your rights as a research participant, you should contact *[insert name or title of person on the IRB/EC or other organization appropriate for the site]* at *[insert physical address and telephone number]*.

What is the cost of study participation?

There is no cost to you for being in this study. You will receive *[insert local amount]* for your time, effort, and travel to and from the clinic for each study visit. You will be offered condoms and lubricants, free of charge at each visit.

Phase II Safety and Acceptability of an Investigational Injectable Product, TMC278 LA, for PrEP (HPTN 076)

**Final Version 2.0
1 October 2014
DAIDS Document ID: 11944**

**US National Institute of Allergy and Infectious Diseases (NIAID)
US National Institutes of Health (NIH)**

Sponsor: NIH, NIAID, DAIDS

**SAMPLE SCREENING AND ENROLLMENT INFORMED CONSENT FORM SIGNATURE
PAGE**

INVESTIGATOR OF RECORD: *[insert name]*
PHONE: *[insert number]*

SIGNATURE PAGE

Study Participation

If you have read this consent form, or had it read and explained to you, and you understand the information, and you voluntarily agree to join the study, please sign your name or make your mark below.

_____	_____	_____
Participant Name (print)	Participant Signature	Date

For staff: I have explained the purpose of the screening to the volunteer and have answered all of her questions. To the best of my knowledge, she understands the purpose, procedures, risks and benefits of this study.

_____	_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature	Date

Samples Stored for Future Testing

Blood:

- _____ My initials indicate that any leftover blood samples may be stored for future testing after study-related testing has been completed.
- _____ I do not agree to allow leftover blood samples to be saved for long-term storage and future testing after study-related testing has been completed.

Swabs/Fluids:

- _____ My initials indicate that any leftover swabs/fluids may be stored for future testing after study-related testing has been completed.
- _____ I do not agree to allow leftover swabs/fluids to be saved for long term storage and future testing after study-related testing has been completed.

SAMPLE TISSUE SUBSET INFORMED CONSENT FORM

Phase II Safety and Acceptability of an Investigational Injectable Product, TMC278 LA, for PrEP (HPTN 076)

Final Version 2.0
1 October 2014
DAIDS Document ID: 11944

Study Implementers:

Division of Infectious Diseases, UMDNJ-New Jersey Medical School, Newark, NJ, USA;
Bronx Prevention Center, Columbia University, Bronx, NY, USA

Study Sponsors: NIH, Division of AIDS (DAIDS), US National Institute of Allergy and Infectious Diseases (NIAID). Study drug is provided by Janssen Pharmaceuticals.

IND Holder: PATH Drug Solutions (PDS)

PRINCIPAL INVESTIGATOR: [Insert Name]

PHONE: [Insert Number]

INTRODUCTION

You are already participating in a research study to find out two things: 1) if a new drug that may prevent HIV infection is safe, and 2) whether women are willing to receive injections (shots) of the new drug. About 24 women are also being asked to provide an additional tissue sample at either the Week 36 or Week 44 visit.

There may be no direct benefits for you if you decide to provide a tissue sample. There also may be some risks with providing a tissue sample. Before you can make an informed decision, you should understand the possible risks and potential benefits of providing a tissue sample. The process of explaining the risks and benefits is called informed consent. This document will describe what will happen during the tissue collection process. This form might have some words in it that are not familiar to you. Please ask us to explain anything that you do not understand before you sign this form. If you tell us that you understand process of providing tissue and fluid samples, you will be asked to read, sign, and date this form. You will also be offered a copy of this form to keep.

Tissue Collection Purpose

The researchers are interested in collecting tissue samples to help them better understand the effects on the human body of the injected study drug.

What happens if you do not want to take part?

Before you learn more about the collection of tissue samples, it is important that you know the following:

- You do not have to agree to provide a tissue sample.
- If you agree to provide a tissue sample but later decide later you want to stop, you can stop at any time during the process.
- Whether or not you take part in this study, you will still continue to receive the same services you get at [insert clinic].

What will happen if you do want to take part?

If you decide to provide a tissue sample, you will need to agree to allow us to do the following prior to enrolling into the tissue subset:

- either confirm that you have had a normal Pap test in the last year, or you need to allow us to perform the exam, and
- test your blood to make sure it clots normally.

If you decide to provide a tissue sample, you will need to agree to allow us to do the following during the Week 36 or Week 44 visit of the main study:

- take a small sample of tissue from your vagina.

What happens during a Pap test?

You have probably had a Pap test before. This test is done routinely for women to check them for cervical cancer. The cervix is part of the female reproductive tract and is at the end of the vagina. If the study team can document that you have a normal Pap test in the last year, we will not need to do a Pap test.

If we cannot document a normal Pap test, you will be offered the test. During a Pap test, you will need to undress and lie down on an exam table. You will place your feet in the exam table stirrups. The clinician will insert a speculum into your vagina to hold it open. Next, cervical tissue will be collected by the clinician with a long swab. The clinician will let you know the results of the Pap test when they are available. If your test is normal, you may be eligible for the tissue biopsy. If your test indicates that additional testing is needed, the clinician will refer you for appropriate care.

What happens during the blood clotting testing?

We will take a blood sample and make sure that your blood clots normally. If the blood does clot normally during the testing, then we would not expect you to bleed more than other women might when the small amount of vaginal tissue is removed.

If the blood does not clot normally then we will not remove any vaginal tissue because we would not want to cause you to bleed more than other women. You will not be able to participate in this part of the study if your clot study is abnormal.

What happens during the tissue collection process?

To minimize risk of infection and bleeding after the tissue biopsy, you must not have vaginal intercourse or put anything in your vagina for three days before the procedure and seven days after the procedure.

The tissue collection process will take about XX minutes. The appointment will be similar to the visits you may have had with your regular gynecologist. A study doctor will insert a speculum into your vagina. A small amount of vaginal tissue will be removed. The tissue sample will be used to help researchers understand how the study drug works in a woman's body and in the vaginal tissue.

Sample Storage

Vaginal tissue samples will be sent to designated laboratories in the United States to test for rilpivirine and to study how the drug is processed in your body.

Leftover Samples

There may be some leftover tissue after all of the study testing has been completed. We would like to use these samples for future research studies related to HIV treatment and prevention. Before your leftover samples could be used we would have to ask for approval from the leadership group of the HIV Prevention Trials Network (HPTN).

If you do not agree to have your leftover samples stored, you can still provide a tissue sample. If you agree to store your samples but change your mind later, you can contact study staff. We will then destroy your samples.

If you agree to this use of your samples, we will ask you to initial the end of this form. Tissue will be sent to designated laboratories in the United States for further testing. Your leftover samples will be stored indefinitely [insert local guidelines]. Any future use or the ability to store your samples longer needs to be reviewed and approved by the NIH and local authorities. If these studies involve other laboratories, we will need approval from your local authorities to store or transfer them elsewhere. Your leftover samples will not be sold or used for commercial reasons.

What are the possible risks or discomforts?

You might feel embarrassed or feel some discomfort during the vaginal tissue collection procedure. It is also possible that after the procedure, you will have some bleeding or that the wound will get infected.

If you experience bleeding, pain, or any unusual vaginal symptoms, contact the clinic right away.

What are the potential benefits?

There may be no direct benefit to you if you decide to provide us with a tissue sample. However, the information learned from the sample may help researchers develop an injectable medicine that prevents HIV.

What are the alternatives to participating?

You do not have to provide us with a tissue sample.

[Sites to amend as applicable] There may be other studies going on at this study clinic or in the community for which you may be eligible. If you wish, we will tell you about other studies that we know about. There may also be other places where you can go for HIV counseling and testing. We will tell you about those places if you wish.

How will your privacy be protected?

Your laboratory test results will be kept private. You will get a unique study identification number that will be used instead of your name on your documents. Only the study staff will be able to see records that identify you by name. This information will not be shared with others. All records will be stored in locked files at the study clinic. Results of your laboratory tests will be made available only to you when you visit the clinic. Your name will never be used in any publication or presentation about the study.

Your records may be reviewed by the sponsor of the study, the US National Institutes of Health (NIH) and their representatives, FDA and other government and regulatory authorities, authorized representatives of PDS and/or its contractors, **[insert name of site]** IRB/EC, study staff, study monitors and [insert applicable local regulatory authorities].

We cannot guarantee absolute confidentiality. [For US sites: In addition to the efforts made by

the study staff to help keep your personal information confidential, we have obtained a Certificate of Confidentiality from the U.S. Federal Government. This certificate protects researchers from being forced to tell people who are not connected with this study, such as the court system, about your participation.

Also, the Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, we will tell the proper authorities.]

A description of this study will be available on www.ClinicalTrials.gov, as required by US law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

Reasons why you may be withdrawn from the tissue and fluid collection process

The process may be ended early without your consent if the study doctor believes that collecting tissue would be harmful to you.

What happens if you are injured by this research?

Taking part in this study may put you at risk for personal injury. Your vagina could bleed where the tissue was collected, or the wound could become infected.

If you experience these problems, study staff will assist you in getting medical care. *[Sites to specify institutional policy:]* It is unlikely that you will be injured as a result of taking part in this study. If you are injured, the *[institution]* will give you the treatment needed for your injuries. You *[will/will not]* have to pay for this treatment. You will be told where you can get additional treatment for your injuries. There is no program to pay money or give other forms of compensation for such injuries through the United States NIH. You do not give up any legal rights by signing this consent form.

Who can you contact if you have any questions?

We are happy to answer any questions that you may have. It may be that you have questions about your rights as a study participant or that you think you have been injured because you were in this study. In this case you can contact [insert name of the investigator or other study staff] at [insert telephone number and physical address].

If you have any questions or concerns about whether you should join this study, or your rights as a research participant, you should contact [insert name or title of person on the IRB/EC or other organization appropriate for the site] at [insert physical address and telephone number].

What is the cost of study participation?

There is no cost to you for being in this study. You will receive [insert local amount] for your time, effort, and travel to and from the clinic for each study visit.

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US National Institutes of Health (NIH)**

Sponsor: NIH, NIAID, DAIDS

SAMPLE TISSUE SUBSET INFORMED CONSENT FORM SIGNATURE PAGE

INVESTIGATOR OF RECORD: *[insert name]*
PHONE: *[insert number]*

SIGNATURE PAGE

Study Participation

If you have read this consent form, or had it read and explained to you, and you understand the information, and you voluntarily agree to join the study, please sign your name or make your mark below.

_____	_____	_____
Participant Name (print)	Participant Signature	Date

For staff: I have explained the purpose of the screening to the volunteer and have answered all of her questions. To the best of my knowledge, she understands the purpose, procedures, risks and benefits of this study.

_____	_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature	Date

**Samples Stored for Future Testing
Vaginal Tissue:**

- _____ My initials indicate that any leftover vaginal tissue samples may be stored for future testing after study-related testing has been completed.
- _____ I do not agree to allow leftover vaginal tissue samples to be saved for long-term storage and future testing after study-related testing has been completed.

SAMPLE FOCUS GROUP INFORMED CONSENT FORM

Phase II Safety and Acceptability of an Investigational Injectable Product, TMC278 LA, for PrEP (HPTN 076)

Final Version 2.0

1 October 2014

DAIDS Document ID: 11944

Study Implementers:

Emavundleni Desmond Tutu HIV Centre, Cape Town, South Africa;
Spilhaus Clinical Research Site, Harare, Zimbabwe;
Division of Infectious Diseases, UMDNJ-New Jersey Medical School, Newark, NJ, USA;
Bronx Prevention Center, Columbia University, Bronx, NY, USA

Study Sponsors: NIH, Division of AIDS (DAIDS), US National Institute of Allergy and Infectious Diseases (NIAID). Study drug is provided by Janssen Pharmaceuticals.

IND Holder: PATH Drug Solutions (PDS)

PRINCIPAL INVESTIGATOR: [Insert Name]

PHONE: [Insert Number]

INTRODUCTION

You have been invited to take part in a focus group with other women that also participated in HPTN 076. About 35-40 women in in both Africa and the United States will participate in focus groups.

The focus group will be led by a trained and experienced group leader. We are interested in learning about your thoughts, opinions, and experiences with being a part of the study, including talking with you about the injections (shots). We would like to know what you didn't like about the injections and what you did like about them. We hope that the information learned from this study will help us to better understand what kind of HIV prevention options women prefer.

What happens if you do not want to join the focus group?

Before you learn more about the study it is important that you know the following:

- You do not have to join the focus group.
- If you join the focus group but later decide later you want to stop, you can stop taking part in the focus group at any time.
- Whether or not you take part in the focus groups, you will still continue to receive the same services you get at [insert clinic].

What will happen if you do want to join the focus group?

If you decide to join the focus group, you will be asked to participate in a XX to XX minute discussion with a trained and experienced group leader. The focus group discussion will not take place during a regular study visit. Instead, it will occur at a separate time somewhere between the Week 44 and Week 76 study visits.

The information that you share during the focus group will be treated confidentially. The focus group will be audio-recorded to help assure that we get the best understanding possible from each focus group meeting. This recording will be used to make a written

transcript of the interview. The recording and transcript will only have a Participant ID number. Your name and any other identifying information that you mention during the focus group discussion will not be associated with your responses. No identifying information will be included in the written transcript. The recording will be destroyed after the study. Although we hope that you will be comfortable answering all of the questions and talking openly and honestly, please keep in mind that you do not have to answer any of the questions. You may stop participating completely at any time.

What are the potential benefits?

You will not receive any direct benefit from being in the focus group; however, you or others in your community may benefit from this study later. The information gathered during this study may help to prevent HIV and other infections. This may be beneficial to you and your community.

What are the possible risks or discomforts?

The questions we will ask you may make you feel uncomfortable. We hope that the focus group procedures described above will minimize your discomfort when discussing sensitive topics. However, the greatest risk may involve your privacy and confidentiality. This is because confidentiality is limited in a focus group setting, since the other members of the focus groups are present during the discussion and we cannot guarantee that they will not discuss what you will say later. Additional steps that the study team has taken to protect your privacy are described below.

How will your privacy be protected?

Every effort will be made to keep your personal information confidential. Your personal information (name, address, phone number) will be protected by the research clinic. Your name, and anything else that might identify you personally, will not be used in any publication of information about this study. We encourage you to make up a name or use a nickname during this focus group.

Your records may be reviewed by the sponsor of the study (US National Institutes of Health (NIH) their representatives, FDA and other government and regulatory authorities, authorized representatives of PDS and/or its contractors, [insert site] IRB, study staff, and study monitors.

We cannot guarantee absolute confidentiality. [For US sites: In addition to the efforts made by the study staff to help keep your personal information confidential, we have obtained a Certificate of Confidentiality from the U.S. Federal Government. This certificate protects researchers from being forced to tell people who are not connected with this study, such as the court system, about your participation.

Also, the Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, we will tell the proper authorities.]

A description of this study will be available on www.ClinicalTrials.gov, as required by US law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

What are the alternatives to participating in this study?

You do not have to participate in the focus group.

Reasons why you may be withdrawn from the study without your consent

Your participation in the focus group may be ended early without your consent for the following reasons:

- The research study, or the focus group part of the research study, is stopped or canceled.
- The study staff feels that participating in the focus group would be harmful to you.

What happens if you are injured by this research?

It is unlikely that you will be injured as a result of taking part in a focus group. If you are injured, the [*institution*] will give you the treatment needed for your injuries. You [*will/will not*] have to pay for this treatment. You will be told where you can get additional treatment for your injuries. There is no program to pay money or give other forms of compensation for such injuries through the United States NIH. You do not give up any legal rights by signing this consent form.

Who can you contact if you have any questions?

We are happy to answer any questions that you may have. It may be that you have questions about your rights as a study participant or that you think you have been injured because you were in this study. In this case you can contact [insert name of the investigator or other study staff] at [[insert telephone number and physical address].

If you have any questions or concerns about whether you should join this study, or your rights as a research participant, you should contact [insert name or title of person on the IRB/EC or other organization appropriate for the site] at [insert physical address and telephone number].

What is the cost of study participation?

There is no cost to you for being in this study. You will receive [insert local amount] for your time, effort, and travel to and from the clinic for each study visit.

**Phase II Safety and Acceptability of an Investigational Injectable Product, TMC278 LA, for
Pre-Exposure Prophylaxis (HPTN 076)**

**Final Version 2.0
1 October 2014
DAIDS Document ID: 11944**

**US National Institute of Allergy and Infectious Diseases (NIAID)
US National Institutes of Health (NIH)**

Sponsor: NIH, NIAID, DAIDS

SAMPLE FOCUS GROUP INFORMED CONSENT FORM SIGNATURE PAGE

INVESTIGATOR OF RECORD: *[insert name]*
PHONE: *[insert number]*

SIGNATURE PAGE

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Study Staff Conducting
Consent Discussion (print)

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Date