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	*Chlamydia trachomatis*
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	*Neisseria gonorrhoeae*
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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A Study of the HIV Prevention Trials Network (HPTN)

Sponsored by:
Division of AIDS, US National Institute of Allergy and Infectious Diseases
US National Institutes of Health

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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Phase II Safety and Acceptability of an Investigational Injectable Product, TMC278 LA, for PrEP

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:	• 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:	• 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:	• 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:	• 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:	• 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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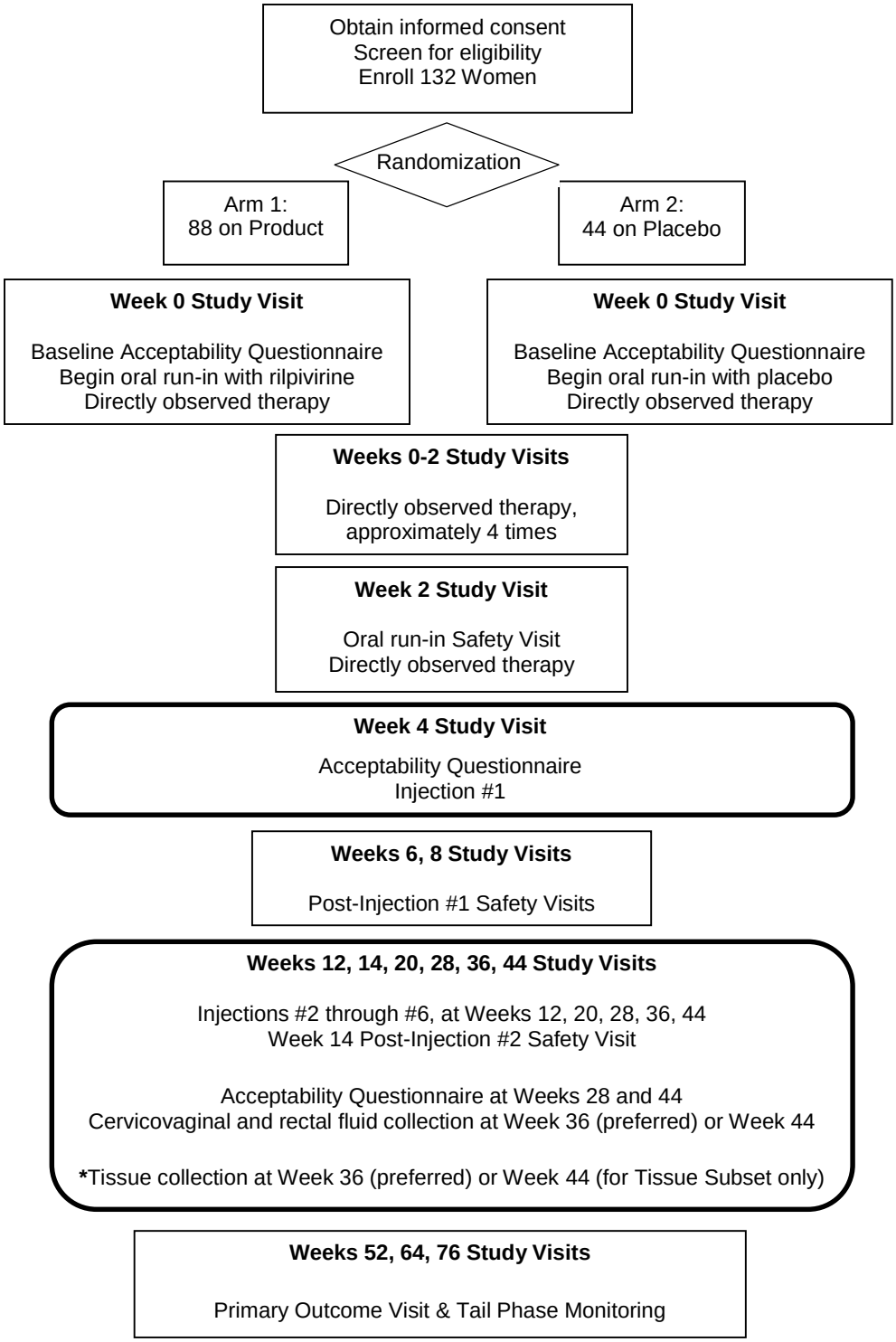
OVERVIEW OF STUDY DESIGN AND RANDOMIZATION SCHEME



***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 term[2] 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) analyses[5-7] 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 prevention[2]

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.[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 10 June 2014, 858 HIV-uninfected and 1052 HIV-infected participants have been dosed with oral TMC278 in clinical trials.

Thirty six Phase I studies were completed in HIV-uninfected participants and two additional Phase I studies were completed in HIV-uninfected special populations.

One Phase I and two Phase IIa studies were completed in HIV-infected participants with oral TMC278. Final efficacy and safety data are available from one Phase IIb study (C204) and from two Phase III studies.[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 26 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. rifampin, carbamazepine) can reduce the TMC278 exposure and should not be co-administered. Drugs that inhibit CYP3A4 activity

(e.g. ketoconazole, boosted protease inhibitors) 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 abstention 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 ISs. 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 ≥ 1,000 cells/mm^3
    - Platelet count ≥ 100,000/mm^3
    - 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 2.0, November 2014, 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 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, hypomagnesia, 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 technic 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 I. 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
- Pregnancy testing (see Section 10.1)*
- 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

*** Pregnancy testing may be performed in the clinic or the laboratory at all visits where this testing is indicated. Testing may be performed using a urine, plasma, or serum sample. The assay used for pregnancy testing must have a limit of detection of 25 mIU/mL or lower. Women not of childbearing potential are excluded from pregnancy testing throughout their participation in this study.**

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:

<u>Administrative and Counseling Procedures</u>

- 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

<u>Clinical Procedures</u>

- Interim medical history (including concomitant medications)

- Symptom-directed physical examination
- Blood collection
- HIV rapid testing
- Urine collection
- Pregnancy testing (see Section 10.1)
- 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
- Pregnancy testing (see Section 10.1)
- 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
- Pregnancy testing (see Section 10.1)
- 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
- Pregnancy testing (see Section 10.1)
- 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 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 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:

<u>Administrative and Counseling Procedures</u>
- Confirm locator information
- Provide HIV risk reduction counseling
- Offer condoms and lubricant
- Provide reimbursement

<u>Clinical Procedures</u>
- Interim medical history (including concomitant medication)
- Symptom-directed physical examination
- AE assessment
- Blood collection

- HIV rapid testing
- Urine collection
- Pregnancy testing (see Section 10.1)
- 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
- Pregnancy