Clinical Protocol

A prospective, randomized, placebo-controlled, three-period crossover, two-way interaction study to evaluate the pharmacokinetics of doravirine and tenofovir disoproxil fumarate on the pharmacokinetics of cross-sex hormonal therapy in adult HIV-negative transgender women

JeffTrial Protocol Number: 15431
Merck MISP Number: 59198

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Study Site: Thomas Jefferson University

Funder: Merck & Co., Inc.

Study Compounds: Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate (DELSTRIGO)
Estradiol
Spironolactone

Phase: 1

Protocol Date: 27 December 2021

PROTOCOL AMENDMENTS AND SUMMARY OF CHANGES

Document	Version Date	Summary of Changes
1.0	24 JANUARY 2020	Original IRB submission
1.1	14 FEBUARY 2020	Revisions based on IRB review
2.0	27 December 2021	Update exclusion criteria, minor typographical corrections

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LIST OF ABBREVIATIONS

AIDS	Acquired Immunodeficiency Syndrome
AE	Adverse Event
ARV	Antiretroviral
AUC_{0-24}	Area under the plasma-concentration time curve from time 0 to 24 hours
AUC_{0-inf}	Area under the plasma-concentration time curve from time 0 extrapolated to infinity
AUC_{0-last}	Area under the plasma-concentration time curve from time 0 to last sampled dose
CBC	Complete Blood Count
CI	Confidence interval
C_{max}	Maximum concentration observed
CMP	Complete Metabolic Panel
CRU	Clinical Research Unit at Thomas Jefferson University
C_{trough}	Trough concentration
CYP	Cytochrome P450
DDI	Drug-Drug Interaction
DOR	Doravirine
ECG	Electrocardiogram
FDA	US Food and Drug Administration
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
IND	Investigational New Drug
mg	Milligram
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
PK	Pharmacokinetics
PrEP	Pre-exposure prophylaxis
QD	Once Daily
SAE	Serious adverse event
SS	Steady State
TGW	Transgender woman
T_{max}	Time of maximum observable plasma concentration
UA	Urinalysis

PROTOCOL SUMMARY

Synopsis	
Transgender women (TGW) living with Human Immunodeficiency Virus (HIV) may prioritize gender-affirming hormonal therapy over antiretroviral (ARV) drug therapy. Hormonal therapy consists of oral estradiol and spironolactone, which induce drug-metabolizing enzymes after prolonged administration. There is limited evidence evaluating the use of hormonal therapy together with HIV ARVs in TGW. TGW living with HIV may prioritize their gender-affirming therapy over ARVs. Doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF) is an ARV approved for the treatment of HIV-1 infection. DOR is primarily metabolized by cytochrome P450 (CYP) 3A with 3TC and TDF having minimal CYP-mediated interactions. A drug interaction study is warranted in light of the 1) inductive effects of hormones on drug metabolizing enzymes, 2) common clearance pathway of DOR/3TC/TDF, and 3) need to understand this interaction in order to enhance the uptake of ARV treatment in TGW living with HIV. This study is designed to evaluate the bi-directional pharmacokinetic interaction between single-dose DOR/TDF in the presence of estradiol in TGW.	
Overview of Study Design	
Randomized, placebo-controlled, three-period crossover, two-way interaction study to evaluate the effect of once-daily DOR/TDF with estradiol/spironolactone in HIV-negative transgender women. Participants will be randomized into two sequences and undergo period specific treatment options. For participants randomized to sequence A, participants will receive DOR/3TC/TDF alone (Period I), placebo and hormone therapy (Period II), and DOR/3TC/TDF and hormone therapy (Period III). In sequence B, participants will receive DOR/3TC/TDF and hormone therapy (Period I), placebo and hormone therapy (Period II), and DOR/3TC/TDF alone (Period 3). There will be a 14-day washout in between periods I and II and II and III.	
Hypothesis	
The mean ratios for estradiol and doravirine/tenofovir disoproxil fumarate (in both directions) will fall below or above the no-effect boundaries defined as 80-125%, respectively.	
Objectives and Endpoints	
Primary Objectives	**Primary Endpoint**
▪ Compare the change in plasma exposure-time profile, defined as $AUC_{(0\text{-last})}$, C_{max}, and C_{trough}, following a single oral dose of DOR/TDF together with estradiol/spironolactone	Change in pharmacokinetic parameters measured as $AUC_{(0\text{-last})}$, C_{max}, and C_{trough}.

▪ Compare the change in plasma exposure-time profile, defined as $AUC_{(0\text{-last})}$, C_{max}, and C_{trough}, following a single oral dose of estradiol together with DOR/TDF	
Secondary Objective	**Secondary Endpoint**
Evaluate the safety and tolerability of DOR/3TC/TDF when co-administered with estradiol and spironolactone	Proportion of Participants with treatment-emergent adverse events for safety parameters
Exploratory Objective	**Exploratory Endpoint**
Evaluate the change in baseline testosterone during the treatment periods	Change in plasma testosterone following treatment

Study Population (Inclusion)

1. Healthy self-identified transgender women (male-to-female) between 18-45 years old at the time of screening
2. Have not undergone an orchiectomy
3. Receiving oral estradiol and spironolactone for $\geq$ 3 months prior to study entry with a self-reported adherence to prescribed doses of $\geq$ 90%
4. Abstain from alcohol consumption throughout the duration of the study
5. Be willing to briefly interrupt hormonal therapy prior to and during the study
6. If on pre-exposure prophylaxis (PrEP) therapy containing tenofovir alafenamide or disoproxil fumarate, willing to discontinue PrEP at least 2 weeks before study start and for the duration of the study
7. Agree to use condoms for all sexual activity prior to the start and throughout the duration of the study
8. Evidence of a personal signed and dated informed consent document indicating that the participant has been informed of all pertinent aspects of the study

Study Population (Exclusion)

1. Presence of clinically significant acute or chronic disease, that in the investigator's opinion, would compromise the participant's safety during the study
2. Current use of any antiretroviral drug. This will not be exclusionary if participants reported discontinuing within 30 days of screening
3. Creatinine clearance $\leq$ 60 mL/min, as estimated by the Cockcroft-Gault equation
4. Known anaphylactic or severe systemic reactions to any components of doravirine, lamivudine, or tenofovir
5. Positive HIV, Hepatitis B or Hepatitis C virus at screening. Evidence of prior Hepatitis B infection and immunity is not exclusionary. Positive hepatitis C antibody with negative viral load or documented antiviral hepatitis C treatment with one post treatment non-detectable hepatitis C viral load is not exclusionary
6. Recent significant blood or plasma donation

7. Concomitant use of drugs, as deemed by the investigator, to have significant drug-drug interactions
8. Received study drug in another study within 4 weeks or within 5 half-lives; whichever occurring first- before first anticipated dose of study drug in this study
9. Unable to refrain from use of over-the-counter, prescription (unless determined appropriate by the investigator), herbal or natural products, vitamins or supplements, or grapefruit juice/grapefruit products
10. Presents any concern by the investigator regarding safe participation in the study or for any other reason the investigator considers the participant inappropriate for participation in the study

Compounds Under Investigation and Doses

Doravirine/lamivudine/tenofovir disoproxil fumarate (Delstrigo)
Class: Antiretroviral
Availability: 100 mg/300 mg/ 300 mg oral tablet
Investigational dosing: 100 mg/300 mg/ 300 mg once-daily

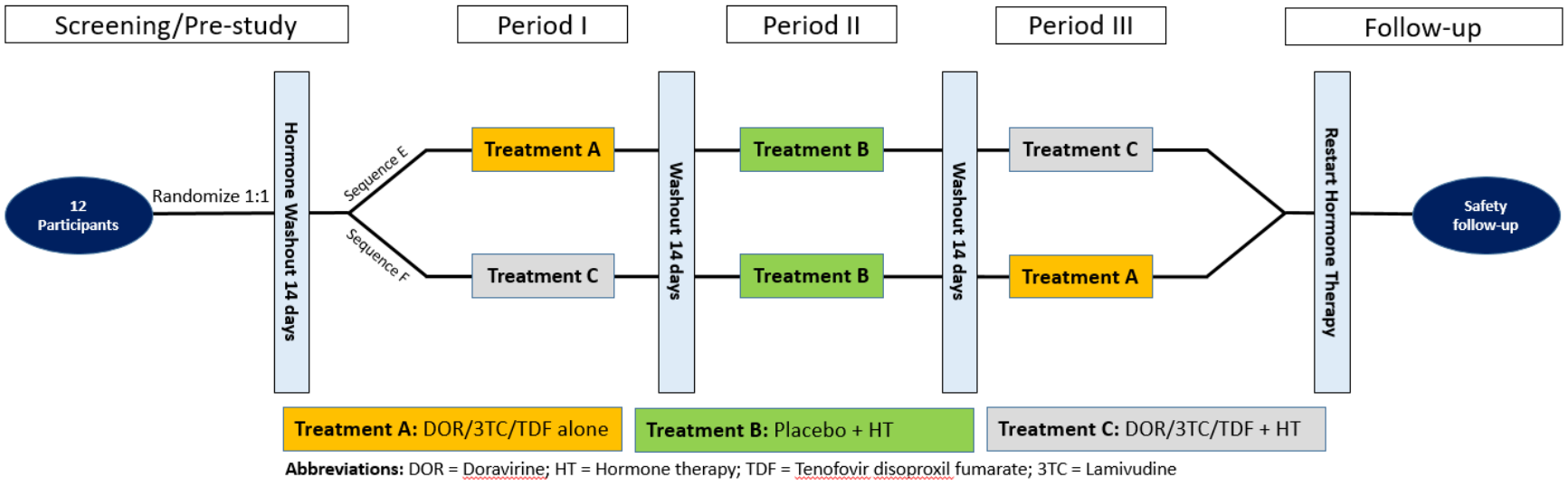
Estradiol (Various)
Class: Feminizing Hormone
Availability: Tablet
Investigational dosing: 8 mg/day

Spironolactone (Various)
Class: Anti-androgen
Availability: Tablet
Investigational dosing: 400 mg/day

Number of Participants

12

Figure 1. Study flow for 12 participants.



SCHEDULE OF EVENTS

Treatment A (DOR/3TC/TDF) – Sequence E (Period I); Sequence F (Period III)																
Procedures		Days														
		Screening (-30)	Pre-study (-14)	Day -1	1							2	3	4	5	Post-Study (7-14 days)
					Pre-dose	PK Sampling (Hours)										
						0	0.5	1	2	6	12	24	48	72	96	
Assessment of Eligibility		X														
Signed Consent Form		X														
Medical History		X		X												
Concomitant Medication Review		X	X	X	X	X						X	X	X	X	X
Randomization				X[1]												
Clinical Laboratory	Complete Blood Count	X		X												X
	Comprehensive Metabolic Panel	X		X												X
	HIV, Hepatitis B & C	X														
	Alcohol & Drug Screen	X		X[3]												
	Urinalysis	X		X												
Clinical Procedure	Physical Exam	X		X												X
	Vital Signs	X		X	X							X				X
	Electrocardiogram	X														
Research Labs	DOR/TDF PK				X		X	X	X	X	X	X	X	X	X	
	Estradiol PK	X		X												
	Total Testosterone	X			X		X	X	X	X		X	X		X	
Treatment	DOR/3TC/TDF					X										
	SOC Hormone Therapy Interruption		X	X												
Assessment of Adverse Events			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inpatient				X[2]	X	----------X						DC				

[1]Subjects will be randomized prior to any dosing (for period 1) after all eligibility criteria, including day -1 procedures are met.

[2]Participants will admitted to the CRU the morning of Day -1 for period I and the afternoon for period III. [3]Urine drug screen only

Abbreviations: DC = Discharge; DOR = Doravirine; HIV = Human Immunodeficiency Virus; PK = Pharmacokinetics; SOC = Standard of care; TDF = Tenofovir Disoproxil Fumarate; 3TC = Lamivudine

Treatment B (Hormone therapy + Placebo) – Sequence E & F (Period II)															
Procedures		Days													
		Screening (-30)	Pre-study (-14)	1								2	3	4	5
				Day -1	Pre-dose	PK Sampling (Hours)									
						0	0.5	1	2	6	12	24	48	72	96
Assessment of Eligibility		X													
Signed Consent Form		X													
Medical History		X		X											
Concomitant Medication Review		X	X	X	X										
Clinical Laboratory	Complete Blood Count	X		X											
	Comprehensive Metabolic Panel	X		X											
	HIV, Hepatitis B & C	X													
	Alcohol & Drug Screen	X		X[4]											
	Urinalysis	X		X											
Clinical Procedures	Physical Exam	X		X[2]											
	Vital Signs	X		X	X							X			
	Electrocardiogram	X													
Research Labs	Estradiol PK	X		X	X[1]		X		X	X	X	X	X	X	X
	Total Testosterone	X			X[1]		X	X	X	X		X	X		X
Treatment	Placebo for DOR/3TC/TDF					X									
	SOC Hormone Therapy Restart			X		X									
	SOC Hormone Therapy Interruption		X												
Assessment of Adverse Events			X	X	X	X	X	X	X	X	X	X	X	X	X
Inpatient				X	X[3]	----------X						DC			

[1]Levels will be taken prior to the second estradiol dose.

[2]Pre-dose Physical Exam may be done up to 24 hours prior to dose.

[3]Participants will admitted to the CRU the afternoon of Day -1 on period II [4] Urine drug screen only

Abbreviations: DC = Discharge; DOR = Doravirine; HIV = Human Immunodeficiency Virus; PK = Pharmacokinetics; SOC = Standard of care; TDF = Tenofovir Disoproxil Fumarate; 3TC = Lamivudine

Treatment C (DOR/3TC/TDF + Hormone Therapy) – Sequence E (Period III); Sequence F (Period I)																
Procedures		Days														Post-Study (7-14 days)
		Screening (-30)	Pre-study (-14)	1								2	3	4	5	
				Day -1	Pre-dose	PK Sampling (Hours)										
						0	0.5	1	2	6	12	24	48	72	96	
Assessment of Eligibility		X														
Signed Consent Form		X														
Medical History		X		X												
Concomitant Medication Review		X	X	X	X											X
Randomization				X												
Clinical Laboratory	Complete Blood Count	X		X												X
	Comprehensive Metabolic Panel	X		X												X
	HIV, Hepatitis B & C	X														
	Alcohol & Drug Screen	X		X[4]												
	Urinalysis	X		X												
Clinical Procedure	Physical Exam	X		X												X
	Vital Signs	X		X	X							X				X
	Electrocardiogram	X														
Research Labs	DOR/TDF PK					X	X	X	X	X	X	X	X	X	X	
	Estradiol PK	X		X	X[2]		X		X	X	X	X	X	X	X	
	Total Testosterone	X			X[2]		X	X	X	X		X	X		X	
Treatment	DOR/3TC/TDF					X										
	SOC Hormone Therapy Restart			X		X										
	SOC Hormone Therapy Interruption		X													
Assessment of Adverse Events			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inpatient				X[3]	X	----------X						DC				

[1]Subjects will be randomized prior to any dosing (for period 1) after all eligibility criteria, including day -1 procedures are met. only [2]Levels will be taken prior to the second estradiol dose.
[3]Participants will admitted to the CRU the morning of Day -1 for period I and the afternoon for period III [4] Urine drug screen. **Abbreviations:** DC = Discharge; DOR = Doravirine; HIV = Human Immunodeficiency Virus; PK = Pharmacokinetics; SOC = Standard of care; TDF = Tenofovir Disoproxil Fumarate; 3TC = Lamivudine

1 INTRODUCTION

1.1 Study Background

1.1.1 Transgender Women and Human Immunodeficiency Virus

It is estimated that 1 million people identify as transgender (both male-to female and female-to-male) in the United States.[1] Transgender is a term for people whose gender identity differs from what is associated with their sex assigned at birth. A transgender woman (TGW) refers to a person who was assigned male at birth but identifies and lives as a woman.[2] The global prevalence of Human Immunodeficiency Virus (HIV) infection is estimated to be 19% among TGW.[3] Transgender women represent approximately 22-28% of the 1.1 million adults living with HIV in the United States with a new diagnosis 3 times the national average.[1] TGW are disproportionally affected, as they are 49 times more likely to be infected with HIV compared to the general population.[3] Furthermore, HIV infections are more prevalent in TGW compared to transgender men (21% vs. 1.2%, respectively) with approximately 70% of TGW with HIV being Black or Hispanic.[1,4,5] These national and global estimates may be underestimates as a result of stigma, discrimination, social rejection, healthcare provider insensitivity to transgender issues, and exclusion preventing adequate access to healthcare.

1.1.2 Gender Affirming Feminizing Hormone Therapy

Not all individuals who identify as a TGW seek gender affirming feminizing hormone therapy. For those who decide to undergo treatment, the Endocrine Society and the Center of Excellence for Transgender Health at the University of California, San Francisco have issued guidance on initiating and monitoring feminizing hormone therapy. Common hormone regimens in TGW include estrogens, antiandrogens, and progesterone. 17β-estradiol is the bioidentical hormone produced in the ovary and is the most common estrogen used in feminizing therapy. Oral, transdermal, and parenteral routes of administration for 17 β-estradiol are available. Spironolactone and 5-alpha reductase inhibitors are among the common oral antiandrogens used to block the effects of testosterone or suppress its production, respectively. Serum estradiol and testosterone are used to monitor therapy with recommendations to maintain physiological levels between 100-200 pg/mL and <50 ng/dL, respectively.[2] It is estimated that 70% of TGW use non-injection hormones with 33% who use injectable hormone therapy in the United States.

1.1.3 Management of Human Immunodeficiency Virus Infection in Transgender Women

Antiretroviral (ARV) therapy is recommended to individuals infected with HIV to prevent progression to immunodeficiency, premature death, and transmission. Initial therapy generally consists of two nucleoside reverse transcriptase inhibitors (NRTI) in combination with other ARV classes such as integrase strand transfer inhibitor, protease inhibitors or non-nucleoside reverse transcriptase inhibitors (NNRTIs).[6] Of the NRTIs, TGW living with HIV were reported to most frequently use tenofovir (79%) with 23% using abacavir.[7] Twenty-eight percent reported using an NNRTI based regimen. NNRTIs, such as doravirine (DOR), may be an optimal choice for some TGW based on its low potential for drug-drug interaction (DDI), tolerability, and availability as a

once-daily fixed-dose regimen together with lamivudine (3TC) and TDF. The favorable metabolic profile of DOR makes it favored in those with dyslipidemias, especially since TGW are at a higher risk for cardiovascular events due to HIV infection and hormone therapy.[8-10]

A recent cross-sectional study by Braun et al. has raised concerns over suboptimal ARV adherence in TGW living with HIV on feminizing hormone therapy.[7] Of the half of study participants who were living with HIV, 57% were concerned with the DDI potential with 40% reporting not using ARVs, hormone therapy, or both because of this concern.

1.1.4 Overview of Doravirine/Lamivudine/Tenofovir disoproxil fumarate (DOR/3TC/TDF)

Doravirine is a novel NNRTI approved for use in patients with HIV-1 in combination with 3TC and TDF. The pharmacokinetics of doravirine is expected to be similar between healthy volunteers and those living with HIV-1. DOR/3TC/TDF is a complete regimen for the treatment of HIV-1 infection in adult patients with no prior ARV treatment or replacement of current stabilized ARV treatment.

1.1.5 Mechanism of Interaction

It is unclear what chronic hormone therapy with estradiol in TGW will do to the clearance mechanisms involved in ARV elimination. Evidence from in-vitro animal and human models have shown that chronic elevated exposures of 17β -estradiol induce phase I and II drug metabolizing enzymes through enhancing major transcription factors that regulate the expression of drug metabolizing enzymes.[11-13] Similarly, the metabolite 17β-estradiol glucuronide, has been shown to regulate multidrug resistance-associate protein 2 (MDR2) regulation, which was associated with changes in transporter activity in in-vitro human intestinal cells.[14] In addition, spironolactone is also implicated as an inducer for drug metabolic enzymes and transporters based on in-vitro and in-vivo animal studies through mechanisms similar to estradiol.[15-17]

Working with the hypothesis that high-dose chronic administration of estradiol and spironolactone may alter ARV drug clearance through cytochrome or transporter mechanisms, ARV exposure may indeed be compromised in TGW. A recent PK study in TGW presented at the 2018 International AIDS Conference may confer insight to this interaction.[18] The iFACT study observed a 13% reduction in the TDF exposure with concurrent feminizing hormone therapy with no change in hormone levels. The authors concluded that there were no significant interactions in both directions. However, the results of this study may not be generalizable to TGW in the US. First, due to its fixed-sequence design, the study was unable to estimate the within-participant variability in drug exposure or designed to test no-effect boundaries. Second, the inductive effects from high dose hormone therapy may not have been truly witnessed given that TGW enrolled were just beginning hormone therapy or had not received hormones within the past 6 months.

1.1.6 Overview of Gender Affirming Feminizing Hormone Therapy

1.1.6.1 17-β Estradiol

Oral 17-β Estradiol (estradiol) is the most common hormone used for feminizing therapy. Estradiol is the bioidentical hormone to that of the human ovary. Titration upwards over 3-6 months together with laboratory monitoring for estradiol and testosterone levels over time is common practice.

1.1.6.2 Spironolactone

Anti-androgens are used alongside estradiol to reduce masculinization and reduce testosterone levels. Spironolactone is the most commonly used anti-androgen in the United States. Suppression of testosterone production minimizes and suppresses male secondary sexual characteristics and lowers estradiol dosing.

1.2 Study Population and Dosing Rationale

1.2.1 Rationale for Study Population

Clinical research in the TGW population is limited. There is a high burden of HIV in TGW that is disproportional to cisgender men and women. In the United States, the rate of new diagnosis for HIV infection is 3 times greater than the national average. TGW are less likely to seek access to healthcare for the fear of stigma, insensitivity, and discrimination. Despite the availability of pre-exposure prophylaxis (PrEP), concerns arise when it is co-administered with hormone therapy reducing uptake of PrEP among TGW. Moreover, those living with HIV are less likely to take ARVs or maintain adequate viral load suppression as TGW may prioritize hormone therapy first for fear that ARVs may compromise hormone therapy.

1.2.2 Rationale for Dose Selection

1.2.2.1 DOR/3TC/TDF

DOR/3TC/TDF 100 mg/300 mg/300 mg was selected based on the approved doses marketed in the United States.

1.2.2.2 17-β Estradiol

A maximum dose of 8mg/day oral estradiol was selected based on the Guidelines for the Primary and Gender-Affirming Care of Transgender and Gender Nonbinary People published by the UCSF Transgender care at the University of California.[19]

1.2.2.3 Spironolactone

A maximum dose of 400 mg/day oral spironolactone was selected based on the Guidelines for the Primary and Gender-Affirming Care of Transgender and Gender Nonbinary People published by the UCSF Transgender care at the University of California.

1.3 Rationale for Endpoints

1.3.1 Pharmacokinetic/Pharmacodynamic Endpoints

For estradiol, plasma estradiol concentrations were selected to estimate the PK parameters for estradiol exposure during feminizing hormone therapy. Serial PK sampling will determine the

interaction potential between DOR/3TC/TDF over a period of one dosing interval for both drugs.

For DOR/TDF, plasma DOR/TDF concentrations were selected to estimate the PK parameters for DOR/3TC/TDF exposure when co-administered with hormone therapy. Serial PK sampling will determine the interaction potential between estradiol and DOR/TDF over a period of one dosing interval for both drugs.

1.3.2 Safety Endpoints

The safety for DOR/3TC/TDF, estradiol, and spironolactone has been established. This study will observe the safety and tolerability following co-administration with feminizing hormone therapy in healthy transgender women. Given the extensive experience of these drugs, it is not expected that the current study will be sensitive to detect new or uncommon safety events associated with co-administration.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objectives

- Evaluate the plasma concentration-time profile, defined as $AUC_{(0\text{-last})}$, $AUC_{(0\text{-inf})}$, and C_{max} of estradiol when co-administered with doravirine/lamivudine/tenofovir disoproxil fumarate.
- Evaluate the plasma concentration-time profile, defined as $AUC_{(0\text{-last})}$, $AUC_{(0\text{-inf})}$, and C_{max}, of doravirine and tenofovir disoproxil fumarate when co-administered with estradiol and spironolactone.

2.1.2 Secondary Objective

- Evaluate the safety and tolerability of doravirine/lamivudine/tenofovir disoproxil fumarate when co-administered with estradiol and spironolactone in transgender women.

2.1.3 Exploratory Objective

- Evaluate the change in plasma testosterone when doravirine/lamivudine/tenofovir disoproxil fumarate is co-administered with estradiol.

2.2 Endpoints

2.2.1 Primary Endpoint

- Change in the estradiol plasma concentration-time profile, as defined by $AUC_{(0\text{-last})}$, $AUC_{(0\text{-inf})}$, and C_{max}
- Change in the doravirine and tenofovir disoproxil fumarate plasma concentration-time profile, as defined by $AUC_{(0\text{-last})}$, $AUC_{(0\text{-inf})}$, and C_{max}

2.2.2 Secondary Endpoint

Proportion of Participants experiencing adverse event(s) characterized by type, frequency, severity, timing and laboratory abnormalities- and tolerability of the co-administered drugs.

2.2.1 Exploratory Endpoint

Change in plasma testosterone following doravirine/lamivudine/tenofovir disoproxil fumarate administration

3 STUDY DESIGN

This is a prospective, single-center, placebo-controlled, three-period, cross-over, pharmacokinetic study investigating the bi-directional pharmacokinetic effect between doravirine/lamudine/tenofovir disoproxil fumarate and cross-sex hormones.

Twelve healthy HIV-negative adult participants who identify as a transgender woman will be enrolled.

Participants will be randomized into two sequences (6 participants per sequence). Participants will undergo treatment specific groups for each period with a 14-day washout in between periods I and II and II and III. In treatment A, a single dose of DOR/3TC/TDF 100 mg/300 mg/300 mg will be administered alone. Participants will be dosing their standard-of-care hormone regimens together with placebo in treatment B. Lastly, Treatment C will be co-administration of DOR/3TC/TDF 100 mg/300 mg/300 mg together with standard-of-care hormone therapy. **Figure 1** displays the study schematic.

4 PARTICIPANT SELECTION

4.1 Inclusion Criteria

Participant eligibility should be reviewed and documented by an appropriate member of the investigator's study team before patients are included in the study.

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Healthy self-identified transgender women (male-to-female) between 18-45 years old at the time of screening
2. Have not undergone an orchiectomy
3. Receiving oral estradiol and spironolactone for $\geq$ 3 months prior to study entry with a self-reported adherence to prescribed doses of $\geq$ 90%
4. Abstain from alcohol consumption throughout the duration of the study
5. Be willing to briefly interrupt hormonal therapy prior to and during the study
6. If on pre-exposure prophylaxis (PrEP) therapy containing tenofovir alafenamide or disoproxil fumarate, willing to discontinue PrEP at least 2 weeks before study start and for the duration of the study

7. Agree to use condoms for all sexual activity prior to the start and throughout the duration of the study
8. Evidence of a personal signed and dated informed consent document indicating that the participant has been informed of all pertinent aspects of the study

4.2 Exclusion Criteria

Participants with any of the following characteristics or conditions will not be included in the study:

1. Presence of clinically significant acute or chronic disease, that in the investigator's opinion, would compromise the participant's safety during the study
2. Current use of any antiretroviral drug. This will not be exclusionary if participants reported discontinuing within 30 days of screening
3. Creatinine clearance $\leq$ 60 mL/min, as estimated by the Cockcroft-Gault equation
4. Known anaphylactic or severe systemic reactions to any components of doravirine, lamivudine, or tenofovir disoproxil fumarate
5. Positive HIV, Hepatitis B or Hepatitis C virus at screening. Evidence of prior Hepatitis B infection and immunity is not exclusionary. Positive hepatitis C antibody with negative viral load or documented antiviral hepatitis C treatment with one post treatment non-detectable hepatitis C viral load is not exclusionary
6. Recent significant blood or plasma donation
7. Concomitant use of drugs, as deemed by the investigator, to have significant drug-drug interactions
8. Received study drug in another study within 4 weeks or within 5 half-lives; whichever occurring first- before first anticipated dose of study drug in this study
9. Unable to refrain from use of over-the-counter, prescription (unless determined appropriate by the investigator), herbal or natural products, vitamins or supplements, or grapefruit juice/grapefruit products
10. Presents any concern by the investigator regarding safe participation in the study or for any other reason the investigator considers the participant inappropriate for participation in the study

4.3 Study Drug and Adherence

Enrolled participants must be willing and able to adhere to the following lifestyle restrictions during the course of the study in order to be eligible for participation:

1. If drinks alcohol, participant should have $\leq$ 3 drinks per day
2. With the exception of marijuana, illicit drugs, should be avoided throughout the study duration
3. Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements, unless at the opinion of the investigator, not compromise the safety of the participant

4.4 Participant Discontinuation and Withdrawal

Participants may withdraw consent at any time for any reason. In addition, a participant may be withdrawn by the investigator if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Participants who miss any treatment dose will be discontinued from the study. Any participant who suffers a serious safety adverse events possibly- or probably-related-to study intervention will be discontinued. If more than three participants are discontinued due to possibly- or probably-related-to study intervention, the study will be terminated.

4.4 Participant Replacement Strategy

If a participant discontinues from the trial, a replacement participant may be enrolled if deemed appropriate by the investigators. The replacement participant will undergo the same treatment sequence (as appropriate) as the participant being replaced beginning at period I through period III.

5 STUDY INTERVENTIONS

5.1 Treatment Drugs

A fixed-dose combination product, doravirine/lamivudine/tenofovir disoproxil fumarate, will be used in this study. Participants will be using their standard of care hormone therapy consisting of estradiol and spironolactone.

Table 1 highlights the dose, frequency, route of administration, and protocol regimen under investigation.

Table 1: Dose, frequency, route of administration, and protocol regimen under investigation

Drug	**Maximum Dose during the study**	**Dosage Form**	**Dosing Frequency**	**Route of Administration**	**Protocol Regimen**
Doravirine/ Lamivudine/ Tenofovir disoproxil fumarate	100 mg/ 300 mg/ 300 mg	Tablet	Once-daily for one dose	Oral	One time dose for treatment groups A & C
Estradiol	8 mg	Tablet	4 mg twice-daily for two doses	Oral	One time dose for treatment group B & C
Spironolactone	400 mg	Tablet	200 mg twice-daily for two doses	Oral	One time dose for treatment group B & C

Placebo	NA	Tablet	Once-daily for one dose	Oral	One time dose for treatment group B

5.2 Treatment Allocation

Participants will be screened using a screening number (SN) consisting of an alpha-numeric code starting with SN 1001. Allocation numbers will begin with 201. Replacement Participants will begin with allocation 301.

6 STUDY PROCEDURES

6.1 Overview

Procedures to be performed at each visit are summarized on the table of scheduled events. It may be necessary to perform study procedures at unscheduled time points if deemed clinically necessary by the investigator. Additional evaluations/testing may be deemed necessary by the investigator and or sponsor for reasons related to Participant safety.

Trial procedures should be completed as close to the prescribed/scheduled time as possible. Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

6.2 Informed Consent

Consent must be documented by the participant's dated signature on a consent form along with the dated signature of the person conducting the consent discussion. A copy of the signed and dated consent form will be given to the participant before participation in the trial. The participant will be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the trial. The informed consent will adhere to institutional review board (IRB) requirements, applicable laws and regulations.

6.2 Participant Recruitment and Screening

Participants will be recruited through Jefferson Marketing Media advertisement.. Within approximately 4 weeks prior to randomization, potential participants will be evaluated to determine that they fulfill the entry requirements. Informed consent will be obtained from participants who elect to participate in the study. Consent form must be signed before any study related procedures are done. Participants will be asked to fast from food and drink, except water, for at least 8 hours prior to the screening visit labs being drawn. The following procedures/assessments will be performed during the screening visit:

- Medical history
- Vital signs
- Physical examination
- Electrocardiogram (ECG)
- Concomitant medication review

- Laboratory safety tests including:
  - Complete blood count with differential and complete metabolic panel
- Hepatitis B surface antigen, Hepatitis C antibody and HIV tests
- Estradiol and testosterone level
- Urine drug screen
- Urinalysis
- Estradiol/testosterone level

6.3 Study Visit Schedule

In addition to the procedures and assessments detailed below- adverse events and concomitant medication will be assessed. Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

6.3.1 Treatment A (Sequence E, Period I): Administration of DOR/3TC/TDF Alone

- **Study Day -14**
  Participants will be scheduled to discontinue their hormone therapy -14 days before the initial study start date. Participants will be randomized 1:1 to either sequence E or F.

- **Study Day -1**
  Participants will report to the CRU in the morning. The following procedures/assessments will be performed:
  - Urine drug screen
  - Lab Safeties
  - Urinalysis
  - Physical exam
  - Vital signs
  - Estradiol PK

- **Study Day 1**
  Assessments: Vital signs, adverse events, and concomitant medication review prior to dosing
  Pre-Dose PK: A PK will be drawn prior to dosing of DOR/3TC/TDF (time 0 = pre-dose), Physical exam (may be done up to 24 hours prior to dose)
  Pre-Dose Research Labs: Total testosterone will be drawn prior to dosing DOR/3TC/TDF (time 0 = pre-dose)
  Dosing: Participants will be given only DOR/3TC/TDF (100mg/300mg/300mg) with 8 ounces of water in the morning following an 8-hour overnight fast.
  Post-Dose PK: PK will be drawn 0.5, 1, 2, 6, and 12 hours post study day 1 dose
  Post-Dose Research Labs: Total testosterone will be drawn following DOR/3TC/TDF dose at 0.5, 1, 2 and 6 hours post study day 1 dose

- **Study Day 2**
  Assessments: Adverse events and concomitant medication review
  Post-Dose PK: PK will be drawn 24 hours post study day 1 dose
  Post-Dose Research Labs: Total testosterone will be drawn 24 hours post study day 1 dose
  Participants will be discharged from the CRU following assessments and 24 hour post-dose PK

- **Study Day 3**
  Participants will arrive in the morning to the CRU
  Assessments: Adverse events and concomitant medication review
  Post-Dose PK: PK will be drawn 48 hours post study day 1 dose
  Post-Dose Research Labs: Total testosterone will be drawn 48 hours post study day 1 dose
  Participants will be discharged from the CRU following assessments and procedures

- **Study Day 4**
  Participants will arrive in the morning to the CRU
  Assessments: Adverse events and concomitant medication review
  Post-Dose PK: PK will be drawn 72 hours post study day 1 dose
  Post-Dose Research Labs: Total testosterone will be drawn 72 hours post study day 1 dose
  Participants will be discharged from the CRU following assessments and procedures

- **Study Day 5**
  Participants will arrive in the morning to the CRU
  Assessments: Adverse events and concomitant medication review
  Post-Dose PK: PK will be drawn 96 hours post study day 1 dose
  Post-Dose Research Labs: Total testosterone will be drawn 96 hours post study day 1 dose
  Participants will be discharged from the CRU following assessments and procedures and advised to not use hormone therapy for a washout period of 14 days

6.3.2 Treatment A (Sequence F, Period III): Administration of DOR/3TC/TDF Alone

- **Study Day -14**
  Participants will have a 14 day washout from Period II prior to entry into period III

- **Study Day -1**
  Participants will report to the CRU in the evening. The following procedures/assessments will be performed:
  - Urine drug screen
  - Urinalysis
  - Physical exam
  - Vital signs
  - Estradiol PK

- **Study Day 1**
  Assessments: Vital signs, adverse events, and concomitant medication review prior to dosing
  Pre-Dose PK: A PK will be drawn prior to dosing of DOR/3TC/TDF (time 0 = pre-dose)
  Pre-Dose Research Labs: Total testosterone will be drawn prior to dosing DOR/3TC/TDF (time 0 = pre-dose)
  Dosing: Participants will be given only DOR/3TC/TDF (100mg/300mg/300mg) with 8 ounces of water in the morning following an 8-hour overnight fast.
  Post-Dose PK: PK will be drawn 0.5, 1, 2, 6, and 12 hours post study day 1 dose
  Post-Dose Research Labs: Total testosterone will be drawn following DOR/3TC/TDF dose at 0.5, 1, 2 and 6 hours post study day 1 dose

- **Study Day 2**
  Assessments: Adverse events and concomitant medication review
  Post-Dose PK: PK will be drawn 24 hours post study day 1 dose
  Post-Dose Research Labs: Total testosterone will be drawn 24 hours post study day 1 dose
  Participants will be discharged from the CRU following assessments and 24 hour post-dose PK

- **Study Day 3**
  Participants will arrive in the morning to the CRU
  Assessments: Adverse events and concomitant medication review
  Post-Dose PK: PK will be drawn 48 hours post study day 1 dose
  Post-Dose Research Labs: Total testosterone will be drawn 48 hours post study day 1 dose
  Participants will be discharged from the CRU following assessments and procedures

- **Study Day 4**
  Participants will arrive in the morning to the CRU
  Assessments: Adverse events and concomitant medication review
  Post-Dose PK: PK will be drawn 72 hours post study day 1 dose
  Post-Dose Research Labs: Total testosterone will be drawn 72 hours post study day 1 dose
  Participants will be discharged from the CRU following assessments and procedures and advised to restart hormone therapy

- **Study Day 5**
  Participants will arrive in the morning to the CRU
  Assessments: Adverse events and concomitant medication review
  Post-Dose PK: PK will be drawn 96 hours post study day 1 dose
  Post-Dose Research Labs: Total testosterone will be drawn 96 hours post study day 1 dose
  Participants will be discharged from the CRU following assessments and procedures and advised to restart hormone therapy

6.3.3 Treatment B (Sequence E & F, Period II): Administration of Estradiol & Spironolactone

- **Study Day -14**
  Participants will have a 14 day washout from Period I prior to entry of period II

- **Study Day -1**
  Participants will report to the CRU in the evening. The following procedures/assessments will be performed prior to dosing:
  - Urine drug screen
  - Urinalysis
  - Physical exam
  - Vital signs
  - Estradiol PK

  Dosing: Participants will be given oral estradiol 4 mg and spironolactone 200 mg with 8 ounces of water in the evening following performed procedure/assessments

- **Study Day 1**
  Assessments: Vital signs, adverse events, and concomitant medication review prior to dosing

Pre-Dose PK: A PK will be drawn prior to dosing of estradiol and spironolactone (time 0 = pre-dose)
Pre-Dose Research Labs: Total testosterone and estradiol will be drawn prior to dosing estradiol and spironolactone (time 0 = pre-dose)
Dosing: Participants will be given placebo + estradiol 4 mcg and spironolactone 200 mg with 8 ounces of water
Post-Dose PK: PK will be drawn at 2, 6, and 12 hours post study day 1 dose
Post-Dose Research Labs: Total testosterone will be drawn following estradiol and spironolactone dosing at 0.5, 1, 2, and 6 hours post study day 1 dose

- **Study Day 2**
  Assessments: Adverse events and concomitant medication review
  Post-Dose PK: PK will be drawn 24 hours post study day 1 dose
  Post-dose Research Labs: Total testosterone will be drawn 24 hours post study day 1 dose
  Participants will be discharged from the CRU following assessments and 24 hour post-dose PK

- **Study Day 3**
  Participants will arrive in the morning to the CRU
  Assessments: Adverse events and concomitant medication review
  Post-Dose PK: PK will be drawn 48 hours post study day 1 dose
  Post-Dose Research Labs: Total testosterone will be drawn 48 hours post study day 1 dose
  Participants will be discharged from the CRU following assessments and procedures

- **Study Day 4**
  Participants will arrive in the morning to the CRU
  Assessments: Adverse events and concomitant medication review
  Post-Dose PK: PK will be drawn 72 hours post study day 1 dose
  Post-Dose Research Labs: Total testosterone will be drawn 72 hours post study day 1 dose
  Participants will be discharged from the CRU following assessments and procedures

- **Study Day 5**
  Participants will arrive in the morning to the CRU
  Assessments: Adverse events and concomitant medication review
  Post-Dose PK: PK will be drawn 96 hours post study day 1 dose
  Post-Dose Research Labs: Total testosterone will be drawn 96 hours post study day 1 dose
  Participants will be discharged from the CRU following assessments and procedures and advised to not use hormone therapy for a washout period of 14 days

6.3.1 Treatment C (Sequence F, Period I): Administration of DOR/3TC/TDF + Estradiol/Spironolactone

- **Study Day -14**
  Participants will be scheduled to discontinue their hormone therapy -14 days before the initial study start date. Participants will be randomized 1:1 to either sequence E or F.

- **Study Day -1**

Participants will report to the CRU in the evening. The following procedures/assessments will be performed:

- Urine drug screen
- Urinalysis
- Physical exam
- Vital signs
- Estradiol PK

Dosing: Participants will be given oral estradiol 4 mg and spironolactone 200 mg with 8 ounces of water in the evening following performed procedure/assessments

- **Study Day 1**

  Assessments: Vital signs, adverse events, and concomitant medication review prior to dosing
  Pre-Dose PK: A PK will be drawn prior to dosing of DOR/3TC/TDF + estradiol and spironolactone (time 0 = pre-dose)
  Pre-Dose Research Labs: Total testosterone will be drawn prior to dosing DOR/3TC/TDF (time 0 = pre-dose)
  Dosing: Participants will be given only DOR/3TC/TDF (100mg/300mg/300mg) + estradiol 4 mg and spironolactone 200 mg with 8 ounces of water in the morning following an 8-hour overnight fast.
  Post-Dose PK (Estradiol): PK will be drawn 0.5, 1, 2, and 12 hours post study day 1 dose
  Post-Dose PK (DOR/TDF): PK will be drawn 0.5, 1, 2, 6, and 12 hours post study day 1 dose
  Post-Dose Research Labs: Total testosterone will be drawn following DOR/3TC/TDF dose at 0.5, 1, 2 and 6 hours post study day 1 dose

- **Study Day 2**

  Assessments: Adverse events and concomitant medication review
  Post-Dose PK (DOR/TDF + estradiol): PK will be drawn 24 hours post study day 1 dose
  Post-Dose Research Labs: Total testosterone will be drawn 24 hours post study day 1 dose
  Participants will be discharged from the CRU following assessments and 24 hour post-dose PK

- **Study Day 3**

  Participants will arrive in the morning to the CRU
  Assessments: Adverse events and concomitant medication review
  Post-Dose PK (DOR/TDF + estradiol): PK will be drawn 48 hours post study day 1 dose
  Post-Dose Research Labs: Total testosterone will be drawn 48 hours post study day 1 dose
  Participants will be discharged from the CRU following assessments and procedures

- **Study Day 4**

  Participants will arrive in the morning to the CRU
  Assessments: Adverse events and concomitant medication review
  Post-Dose PK (DOR/TDF + estradiol): PK will be drawn 72 hours post study day 1 dose
  Post-Dose Research Labs: Total testosterone will be drawn 72 hours post study day 1 dose
  Participants will be discharged from the CRU following assessments and procedures and advised to not use hormone therapy for a washout period of 14 days

- **Study Day 5**

Participants will arrive in the morning to the CRU
Assessments: Adverse events and concomitant medication review
Post-Dose PK (DOR/TDF + estradiol): PK will be drawn 96 hours post study day 1 dose
Post-Dose Research Labs: Total testosterone will be drawn 96 hours post study day 1 dose
Participants will be discharged from the CRU following assessments and procedures and advised to not use hormone therapy for a washout period of 14 days

6.3.1 Treatment C (Sequence E, Period III): Administration of DOR/3TC/TDF + Estradiol/Spironolactone

- **Study Day -14**
  Participants will have a 14 day washout from Period I prior to entry of period II

- **Study Day -1**
  Participants will report to the CRU in the evening. The following procedures/assessments will be performed:
  - Urine drug screen
  - Urinalysis
  - Physical exam
  - Vital signs
  - Estradiol PK

  Dosing: Participants will be given oral estradiol 4 mg and spironolactone 200 mg with 8 ounces of water in the evening following performed procedure/assessments

- **Study Day 1**
  Assessments: Vital signs, adverse events, and concomitant medication review prior to dosing
  Pre-Dose PK: A PK will be drawn prior to dosing of DOR/3TC/TDF + estradiol and spironolactone (time 0 = pre-dose)
  Pre-Dose Research Labs: Total testosterone will be drawn prior to dosing DOR/3TC/TDF (time 0 = pre-dose)
  Dosing: Participants will be given only DOR/3TC/TDF (100mg/300mg/300mg) + estradiol 4 mg and spironolactone 200 mg with 8 ounces of water in the morning following an 8-hour overnight fast.
  Post-Dose PK (Estradiol): PK will be drawn 0.5, 1, 2, and 12 hours post study day 1 dose
  Post-Dose PK (DOR/TDF): PK will be drawn 0.5, 1, 2, 6, and 12 hours post study day 1 dose
  Post-Dose Research Labs: Total testosterone will be drawn following DOR/3TC/TDF dose at 0.5, 1, 2 and 6 hours post study day 1 dose

- **Study Day 2**
  Assessments: Adverse events and concomitant medication review
  Post-Dose PK (DOR/TDF + estradiol): PK will be drawn 24 hours post study day 1 dose
  Post-Dose Research Labs: Total testosterone will be drawn 24 hours post study day 1 dose
  Participants will be discharged from the CRU following assessments and 24 hour post-dose PK

- **Study Day 3**
  Participants will arrive in the morning to the CRU

Assessments: Adverse events and concomitant medication review
Post-Dose PK (DOR/TDF + estradiol): PK will be drawn 48 hours post study day 1 dose
Post-Dose Research Labs: Total testosterone will be drawn 48 hours post study day 1 dose
Participants will be discharged from the CRU following assessments and procedures

- **Study Day 4**
  Participants will arrive in the morning to the CRU
  Assessments: Adverse events and concomitant medication review
  Post-Dose PK (DOR/TDF + estradiol): PK will be drawn 72 hours post study day 1 dose
  Post-Dose Research Labs: Total testosterone will be drawn 72 hours post study day 1 dose
  Participants will be discharged from the CRU following assessments and procedures and advised to restart hormone therapy

- **Study Day 5**
  Participants will arrive in the morning to the CRU
  Assessments: Adverse events and concomitant medication review
  Post-Dose PK (DOR/TDF + estradiol): PK will be drawn 96 hours post study day 1 dose
  Post-Dose Research Labs: Total testosterone will be drawn 96 hours post study day 1 dose
  Participants will be discharged from the CRU following assessments and procedures and advised to restart hormone therapy

6.4 Domiciling

Participants will be admitted to the CRU as outlined in the schedule of events.

6.5 Clinical Procedures & Assessments

6.5.1 Medical History

Medical history of Participants participating in the study will be obtained by the investigator or co-investigator(s).

6.5.2 Physical Examination

The full physical examination includes evaluation of the head, eye, ear, nose and throat; the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal and neurological systems. The screening examination will also include height and weight for BMI calculation.

6.5.3 12-Lead Electrocardiogram

Participants will receive an ECG measurement for which they should remain supine for at least 2 minutes.

6.5.4 Vital Signs

Participants should remain supine for at least 2 minutes prior to measurement of vital signs. Measurements include heart rate, blood pressure and respiratory rate. Oral or tympanic temperature will be checked during the screening visit and if needed by the discretion of the physician-investigator, during and after the study.

6.5.5 Laboratory Safety Evaluations

Refer to Appendix 1 for the list of clinical laboratory tests. Laboratory tests will be performed at screening, during and after the study.

- The investigator or medically qualified designee will review the laboratory report, document this review, and record any clinically relevant changes occurring during the study that meet the reporting requirements in the AE section of the CRF. The laboratory reports must be filled with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 7 days after a protocol-specified procedure, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

6.5.6 Prior and Concomitant Medications Review

The investigator or designated personnel will review prior medication, vitamins or supplement use and record prior medication taken by the Participant within 4 weeks before starting the study. All medications, vitamins or supplements, if any, taken from screening visit until the after the study will be recorded.

6.6 Study Restrictions

6.6.1 Diet and Fruit Juice Restriction

Participants must fast from food and drinks with the exception of water for 8 hours prior to the screening visit.

6.6.2 Alcohol Restriction

Alcohol consumption should be avoided during the study. However, if the participant drink alcohol, the participant should have $\leq$ 3 drinks/day.

6.6.3 Smoking Restriction

Participants must continue to avoid smoking throughout the study up until the post-study visit.

6.6.4 Activity Restrictions

Participants will avoid unaccustomed strenuous physical activity (i.e., weight lifting, running, bicycling, etc.) from the screening visit, throughout the trial until the post-trial visit. Participants may participate in light recreational activities during studies (eg, watching television, reading).

6.7 Participant Identification Card

All participants will be given a Participant Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee

will provide the participant with a Participant Identification Card after their written informed consent.

6.8 Standardized Meals

Meals (Breakfast, lunch, dinner and snacks) will be provided to participants during the admission days. Participants will be fasting for at least 8 hours prior to all lab safety and prior to all dosing. Participants will fast 8 hours prior to dosing and 1 hour post dose for all study drugs.

6.9 Study, Drug Dosing, and Procedure Modification Permitted

Modifications to the dose, dosing regimen and clinical or laboratory procedures may be required to achieve the scientific goals of the trial objectives and/or to ensure appropriate safety monitoring of the study Participants. As such, some alterations from the currently outlined schedule may be necessary. Additional laboratory safety tests may be drawn or added to blood samples previously drawn to obtain additional safety information (e.g., creatinine kinase to evaluate elevated AST/ALT). These changes may or may not increase the number of study procedures for a given participant during his/her participation in the entire study.

6.10 Study Stopping Rules

If one or more study participants are discontinued due to a serious safety adverse event, possibly- or probably- related to the study intervention, the study will be halted for review by the investigator along with the medical monitor and in consultation with the Global Pharmacovigilance group at Merck. An independent study physician will be assigned to the study.

7 POTENTIAL RISKS AND BENEFITS

7.1 Potential Risks Associated with Doravirine

The following most common adverse events (for All Grades) have been reported ($\geq$ 5%) with the chronic use of doravirine in patients with HIV infection. The reported adverse event rates reflect chronic daily use together with other ARVs and are derived from large clinical trials in patients with HIV. Although these adverse event rates have been reported in patients, it may be possible that healthy volunteers may also experience these side effects under this protocol.

- **Central nervous system:**
  - Altered sensorium (Doravirine + 3TC + TDF: 4%)
    - Defined as: altered state of consciousness, lethargy, somnolence, syncope
  - Sleep disorders and disturbances (Doravirine + 3TC + TDF: 12%)
    - Defined as: abnormal dreams, hyposomnia, initial insomnia, insomnia, nightmare, sleep disorder, somnambulism
  - Dizziness (Doravirine + 3TC + TDF: 9%)
  - Fatigue (4-6%)
  - Headache (4-6%)
- **Gastrointestinal:**

- Nausea (5-7%)
- Diarrhea (3-5%)

- **Laboratory abnormalities**
  - Total bilirubin 1.1- < 1.6 x ULN (4-5%)

Less commonly reported (≤ 2%) with chronic use of doravirine in patients with HIV on concomitant ARVs include:

- **Dermatologic**
  - Rash (2%)
- **Laboratory abnormalities**
  - Total bilirubin
    - 1.6 - <2.6 x ULN (2%)
    - ≥ 2.6 x ULN (<1%)
  - Creatinine (mg/dL)
    - >1.3- 1.8 x ULN or increase of >0.3 mg/dL above baseline (2-3%)
    - >1.8 x ULN or increase of 1.5 x above baseline (2%)
  - Aspartate aminotransferase (IU/L)
    - 2.5 - <5.0 x ULN (2-4%)
    - ≥ 5 x ULN (<1%)
  - Alanine aminotransferase (IU/L)
    - 2.5 - <5.0 x ULN (3%)
    - ≥ 5 x ULN (<1-1%)
  - Alkaline phosphatase (IU/L)
    - 2.5 - <5.0 x ULN (<1%)
  - Lipase
    - 1.5 - <3.0 x ULN (4-5%)
    - ≥ 3 x ULN (1-3%)
  - Creatine Kinase (IU/L)
    - 6 - <10 x ULN 2%)
    - ≥10 x ULN (2-3%)
  - Cholesterol, fasted (mg/dL)
    - ≥300 mg/dL (<1%)
  - LDL Cholesterol, fasted (mg/dL)
    - ≥190 mg/dL (<1%)
  - Triglycerides, fasted (mg/dL)
    - >500 mg/dL (<1%)

7.1 Potential Risks Associated with Lamivudine

The following most common adverse events (for All Grades) have been reported (≥ 5%) with the chronic use of lamivudine in patients with HIV infection. The reported adverse event rates

reflect chronic daily use together with other ARVs and are derived from large clinical trials in patients with HIV. Although these adverse event rates have been reported in patients, it may be possible that healthy volunteers may also experience these side effects under this protocol.

- **Body as a Whole**
  - Headache (35%)
  - Malaise & fatigue (27%)
  - Fever or chills (10%)
- **Digestive**
  - Nausea (33%)
  - Diarrhea (18%)
  - Nausea & vomiting (13%)
  - Anorexia and/or decreased appetite (10%)
  - Abdominal pain (9%)
  - Abdominal cramps (6%)
  - Dyspepsia (4%)
  - Flatulence (4%)
- **Nervous System**
  - Peripheral neuropathy (5%)
  - Insomnia (4%)
  - Dizziness (3%)
  - Depressive disorders (8%)
- **Respiratory**
  - Pneumonia (3%)
- **Skin**
  - rashes (9%)
- **Musculoskeletal**
  - Musculoskeletal pain (12%)
  - Myalgia (8%)
  - Arthralgia (5%)
- **Laboratory abnormalities**
  - Absolute neutrophil count (<750/mm^3) (15%)

Less commonly reported ($\leq$ 2%) with chronic use of lamivudine in patients with HIV on concomitant ARVs include:

- **Laboratory abnormalities**
  - Hemoglobin (<8 g/L) (2.2%)
  - Platelets (<50,000/mm^3) (2.8%)
  - ALT (>5.0 x ULN) (3.8%)
  - AST (>5.0 x ULN) (4.0%)
  - Bilirubin (>2.5 x ULN) (0.8%)
  - Amylase (>2.0 x ULN) (2.2%)

7.3 Potential Risks Associated with Tenofovir Disoproxil Fumarate

The following most common adverse events (for All Grades) have been reported (≥ 3%) with the chronic use of tenofovir disoproxil fumarate in patients with HIV infection. The reported adverse event rates reflect chronic daily use together with other ARVs and are derived from large clinical trials in patients with HIV. Although these adverse event rates have been reported in patients, it may be possible that healthy volunteers may also experience these side effects under this protocol.

- **Body as a Whole**
  - Headache (8%)
  - Abdominal pain (7%)
  - Back pain (4%)
  - Chest pain (3%)
  - Fever (4%)
- **Digestive**
  - Nausea (11%)
  - Diarrhea (16%)
  - Vomiting (7%)
  - Dyspepsia (5)
- **Nervous System**
  - Neuropathy (12%)
  - Insomnia & other sleep disorders (11%)
  - Dizziness (10%)
  - Depressive disorders (9%)
- **Respiratory**
  - Nasal signs & symptoms (20%)
  - Cough (18%)
- **Skin**
  - Rash (7%)
  - Sweating (3%)
- **Musculoskeletal**
  - Myalgia (4%)
- **Metabolic**
  - Weight loss (4%)
- **Laboratory abnormalities**
  - Triglycerides (>750 mg/dL) (11%)
  - Creatine kinase (M: >990 U/L; F: >845 U/L) (12%)
  - Serum amylase (>175 U/L) (7%)
  - Glycosuria (≥3+) (3%)
  - AST (M: >180 U/L; F: >170 U/L) (4%)
  - ALT (M: >215 U/L; F: >170 U/L) (4%)
  - Serum glucose (>250 U/L) (3%)

Less commonly reported (≤ 2%) with chronic use of tenofovir disoproxil fumarate in patients with HIV on concomitant ARVs include:

- **Laboratory abnormalities**
  - Neutrophils (<750/mm^3) (2%)

10 SAFETY, ADVERSE EVENTS (AE) & SERIOUS ADVERSE EVENTS (SAE)

10.1 Definitions

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 2. Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

10.1.1 Adverse Event (AE)

An adverse event is defined as any untoward medical occurrence in a Participant administered an investigational product that occurs during the conduct of a clinical trial and does not necessarily have a causal relationship with the study drug(s). This can be any unfavorable and unintended physical sign, symptom, laboratory parameter or disease entity that develops or worsens in severity during the course of the trial whether considered related to study drug or not. Adverse events can include any of the following:

- All suspected adverse medication reactions. This includes events possibly related to any concomitant medication use
- Physical Injuries or accidents. If a medical condition is known to have caused the injury or accident (e.g., a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) will be reported as two separate adverse events.
- Abnormalities in physiological testing or physical examination (findings that require clinical intervention or further investigation beyond ordering a repeat [confirmatory] test).
- Drug interactions
- Onset or worsening of preexisting clinical illness
- Laboratory or diagnostic test abnormality that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they are associated

with an already reported clinical event. A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. more frequent follow-up assessments, further diagnostic investigation, etc.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed will be reported if it meets the definition of an adverse event.

All adverse events will be assessed and recorded from the time Participant is enrolled into the study until the post-trial visit. At each contact with the Participant, the investigator or study personnel must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events, including degree of severity and relationship to study agent, should be recorded immediately in the source document.

10.1.2 Serious Adverse Event (SAE)

An SAE is an event that is not an AE per definition above, resulting in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly or any other important medial events. SAEs must be reported using the Serious Adverse Event Form. All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments.

10.2 Assessing and Recording AEs & SAEs

All adverse events, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the participant's last study-related procedure, which may include contact for follow-up of safety.

All adverse events, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g. cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection").

Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported.
During the outpatient phase the Participant will be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement that the Participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)

10.3 Data Safety Monitoring Plan

The investigators will oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above. Independent medical monitoring will include a regular assessment of the number and type of serious adverse events. A Medical Monitor will be assigned to this study. This will be a physician who is not directly involved in the study and is not currently a principal investigator on any other sponsored Merck trial. The role of the Medical Monitor is to review all reportable AEs/SAEs including grading, toxicity assignments, non-reportable AEs, protocol violations/deviations, as well as all other safety data and activity data. The Medical Monitor may recommend reporting of adverse events and relevant safety data, and may also recommend suspension or termination of the study to the investigators and IRB.

11 STATISTICAL AND PHARMACOKINETIC METHODS

11.1 Sample Size Estimation

Sample size was determined from the published within-Participant variability in the pharmacokinetic parameters, AUC and C_{max}, for estradiol, doravirine, and tenofovir disoproxil fumarate **(Table 2)**. A sample size of 10 (G*Power version 3.1.9.2, University of Kiel, Germany) was determined to provide 80% power to reject the null hypothesis that the mean ratios for estradiol and doravirine/tenofovir disoproxil fumarate (in both directions) will fall below or above the no-effect boundaries defined as 80-125%, respectively. The calculation assumes a mean ratio of 1 (no-effect) for the bi-directional interacting drugs with a two-sided significance level of 0.05.

No-effect boundaries were chosen based on the US Food and Drug Administration Guidance on Clinical Drug Interaction Studies. The standard deviation of the paired difference was calculated assuming independence between reference drug (estradiol or doravirine/tenofovir disoproxil fumarate) and co-administered drug. For calculation of standard deviations, a standard normal distribution was assumed for studies with n>60. A t-distribution was used for studies with n≤60.

Table 2. Published within-Participant standard deviations pharmacokinetic parameters and corresponding number of Participants to reject the null hypothesis with 80% power.

Drug	Within-Participant standard deviation		Number of Participants	Reference
	C_{max}	AUC		
Doravrine	0.18	0.17	10	[20]
Tenofovir disoproxil fumarate	0.11	0.09	5	[21]

Estradiol	0.26	0.24	10	[22]

11.2 Pharmacokinetic Analysis

Plasma concentrations of DOR and TDF will be used to calculate the PK parameters for each Participant in the presence or absence of estradiol and spironolactone. Similarly, plasma concentrations of estradiol will be used to calculate the PK parameters for each Participant in the presence or absence of DOR/3TC/TDF.

Analysis will be conducted via a non-compartmental analysis. Parameters of interest include the area under the concentration-time point from time zero extrapolated to infinity ($AUC_{0\text{-}inf}$), $AUC_{0\text{-}last}$, maximum concentration (C_{max}), minimum concentration at 24 hours (surrogate for efficacy), time to maximum concentration (T_{max}), apparent oral clearance (CL/F) and the apparent half-life ($t_{1/2}$) for each participant. The $AUC_{0\text{-}last}$ will be computed using the linear-up, log-down trapezoidal integration method. A log-linear regression using the least-squares method will be employed to estimate other parameters of interest including the terminal half-life generated from the plasma concentration time-curve.

The primary endpoint will be pharmacokinetic and therefore be measured as the exposure parameters $AUC_{0\text{-}last}$, C_{max} and C_{trough}

11.3 Statistical Analysis of Pharmacokinetic Parameters

Estradiol pharmacokinetic parameter estimates computed before and after DOR/3TC/TDF dosing will be compared using a paired student's t-test. Statistical significance will be defined as a p-value <0.05. Geometric mean ratio (GMRs) will be estimated for estradiol. An analysis of variance model will be performed with 90% confidence intervals around the GMRs between reference (estradiol alone) and test (estradiol + DOR/3TC/TDF) will be constructed and compared to the no-effect boundaries (0.8, 1.25).

DOR/TDF pharmacokinetic parameter estimates computed before and after estradiol dosing will be compared using a paired student's t-test. Statistical significance will be defined as a p-value <0.05. Geometric mean ratio (GMRs) will be estimated for DOR/TDF. An analysis of variance model will be performed with 90% confidence intervals around the GMRs between reference (DOR/TDF alone) and test (DOR/3TC/TDF + estradiol) will be constructed and compared to the no-effect boundaries (0.8, 1.25).

11.4 Safety Analysis

Safety and tolerability assessments will be clinically reviewed for any adverse events and include safety lab, vital signs, and physical exam beyond the pre-defined limit of change. Assessment will be performed for all participants enrolled into this study.

Safety results will be summarized and tabulated using descriptive statistics. Results will be reported as the proportion of Participants experiencing an adverse event.

12 ETHICS AND PROTECTION OF HUMAN PARTICIPANTS

12.1 Institutional Review Board Review

The principal investigator must provide the IRB with all appropriate materials, including a copy of the patient informed consent form. The study will not be initiated until the principal investigator obtains written approval of the protocol and the patient ICF from the IRB. Appropriate reports on the progress of this study will be made by the principal investigator to the IRB and medical monitor in accordance with government regulations.

12.2 Informed Consent

The ICH Tripartite Guideline for Good Clinical Practice establishes the general requirements for informed consent. Each participant will be provided with oral and written information in a language they can understand that describes the nature and duration of the study. Before undergoing screening, each Participant must consent in writing to study participation. The Participant will sign and personally date the patient ICF. The person rendering consent will also sign and personally date the ICF as the person who obtained the consent of the Participant. Each Participant will receive a copy of his or her signed ICF.

12.3 Participant Confidentiality

All records will be kept in a locked filing cabinet located in the offices of the Department of Pharmacology and Experimental Therapeutics in 1170 Main Building. All computer entry and networking programs will be performed with coded numbers only; no PHI will be entered into the eCRF. Clinical information will not be released without written permission of the patient, except as necessary for monitoring by the medical monitor, IRB, or the FDA, or other medical practitioner to ensure the safety and appropriate medical management of the patient in the event of a AE/SAE.

13 SUPPORTING DOCUMENTATION

13.1 Appendix 1: Time Windows for Serial Assessments and Dosing

Sampling Window

Sampling Timepoint (Hours)	Sampling Window (Minutes)
Pre-dose (DOR/3TC/TDF, estradiol, and spironolactone)	-30 minutes to 0 hour
> 0 hour – 4 hours	-10 minutes to +10 minutes
> 4 hours – 24 hours	-15 minutes to +15 minutes
> 24 hours – 96 hours	-30 minutes to +30 minutes

Dosing Window

Dosing Timepoint	Dosing Window (Minutes)
DOR/3TC/TDF (Treatment A and Treatment C)	0 hour
Estradiol and Spironolactone (first dose)	0 hour
Estradiol and Spironolactone (second dose)	± 30 minutes from actual 0 hour time. Take this within 5 minutes of DOR/3TC/TDF for TX C.

Pre-Dose Assessment Window

Assessment	Assessment Window (Minutes)
Physical Exam	-24hours
Vital Signs	**-**60 minutes to 0 hour
CBC/Chemistry	-24 hours
Estradiol/Total testosterone(day 1 pre-dose)	-30 minutes to 0 hour
Estradiol/Total testosterone(day 1 post-dose)	Same as DOR/3TC/TDF sampling windows

13.2 Appendix 2: Clinical Laboratory Tests

- Tests detailed in table 3 will be performed by Thomas Jefferson University Hospital – Clinical Chemistry Laboratories
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 3: Protocol required laboratory assessments

Laboratory Assessment	Parameter
Hematology	▪ Platelet count ▪ Hemoglobin ▪ Hematocrit ▪ WBC with differential ▪ Partial thromboplastin time ▪ Prothrombin time
Chemistry	▪ Albumin

	▪ Calcium ▪ Chloride ▪ Bicarbonate ▪ Phosphorus ▪ Potassium ▪ Sodium ▪ Creatinine ▪ Total Bilirubin ▪ Direct bilirubin (If total bilirubin is elevated above the upper limit of normal) ▪ Total protein ▪ Blood urea nitrogen ▪ Glucose ▪ Aspartate Aminotransferase (AST) ▪ Alanine aminotransferase (ALT) ▪ Alkaline phosphatase
Urinalysis	▪ Specific gravity ▪ Microscopic examination (if blood or protein is abnormal) ▪ Blood ▪ Glucose ▪ Specific gravity
Other Laboratory Tests	▪ Serology (Hepatitis B surface antigen [HBsAg] and hepatitis C virus antibody). Hepatitis C viral load may additionally be assessed as confirmation for participants with a positive antibody test ▪ Human immunodeficiency virus screen ▪ Urine drug screen to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines ▪ Blood alcohol level ▪ Testosterone level ▪ Estradiol level

13.3 Appendix 3: Adverse Events: Definitions and procedures for Recording, Evaluating, Follow-up and Reporting

13.3.1 Definition of AE

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the procedural study intervention, whether or not considered related to the procedural study intervention
- An AE can therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the procedural study intervention

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, vital signs, or measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator
- New conditions detected or diagnosed after conduct of the procedural study intervention even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected overdose of a concomitant medication
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology “accidental or intentional overdose without adverse effect.”

Events NOT meeting the AE definition

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

13.3.2 Definition of SAE

- If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met
- An SAE is defined as any untoward medical occurrence that:
    - Results in death
    - Is life threatening
        - The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the

event. It does not refer to an event, which hypothetically might have caused death, if it were more severe

- Requires inpatient hospitalization or prolongation of existing hospitalization
  - Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE. A pre-existing condition is a clinical condition that is diagnosed prior to study intervention and is documented in the participant's medical history.
- Results in persistent or significant disability/incapacity

13.3.3 Additional Events Reported

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable:

- Is a cancer
- Is associated with an overdose of medication

13.3.4 Recording AEs and SAEs

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory and diagnostic reports) related to the event. The investigator will record all relevant AE/SAE information on the AE CRFs at each examination. The investigator will attempt to establish a diagnosis of the vent based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

- An event is definied as "serious" when it meets at least 1 of the pre-defined outcomes as described in the definition of an SAE, not when it is rated as severe
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:
  - **Mild:** An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities
  - **Moderate:** An event that causes sufficient discomfort to interfere with normal everyday activities
  - **Severe:** An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; and both AE and SAE can be assessed as severe

Assessment of causality

The determination of the likelihood that the study intervention caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document that supports the causality noted on the AE form, ensures that medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the study intervention and the AE based upon the available information.

The following components are to be used to assess the relationship between the study intervention and the AE:

- **Time Course:** Did the AE follow in a reasonable temporal sequence from the study intervention?
- **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.
- **Consistency with study intervention:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the procedural study intervention?

The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements. Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a procedural study intervention relationship).

- Yes, there is a reasonable possibility of study intervention relationship:
    - The temporal sequence of the AE onset relative to the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause
- No, there is not a reasonable possibility of procedural study intervention relationship:
    - Temporal sequence of the AE onset relative to study intervention is not reasonable OR the AE is more likely explained by another cause than the study

Follow up of an AE or SAE

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

13.4 Supplemental Material

Lab manual of bio-specimen handling

Bio-specimen sample chain of custody shipment and manifest

Case Report Forms

Source Documents

Data Management and Clinical Monitoring Plan

Pharmacy Repackaging Manual

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