Clinical Protocol

A Phase 1, Open-Label, Fixed-Sequence, Drug Interaction Study to Investigate the Effect of Once-Weekly Rifapentine and Isoniazid on the Pharmacokinetics of Steady-State Doravirine

JeffTrial Protocol Number: 12690
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Study Site: Thomas Jefferson University

Funder: Merck & Co., Inc.

Study Compounds: Doravirine (PIFELTRO)
Rifapentine (PRIFTIN)
Isoniazid

United States Investigational New Drug (IND) Number: 143,072

Phase: 1

Protocol Date: 16 April 2019

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SUMMARY OF PROTOCOL CHANGESVersion	Date	Description
2.0	17 April 2019	1) Addition of FDA stopping rules 2) Enrollment age increased to 60 years-old 3) Addition of pregnancy tests

		4) Clarification of birth control use
1.0	18 February 2019	Original protocol

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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
BID	Twice daily
CBC	Complete Blood Count
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	Confidence interval
C_{max}	Maximum concentration observed
CMP	Complete Metabolic Panel
CRU	Clinical Research Unit at Thomas Jefferson University
CRF	Case report form
C_{trough}	Trough concentration
CYP	Cytochrome P450
DDI	Drug-Drug Interaction
DSMP	Data Safety and Management Plan
eCRF	Electronic case report form
ECG	Electrocardiogram
FDA	US Food and Drug Administration
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Council for Harmonization
IND	Investigational New Drug
INH	Isoniazid
INSTI	Integrase Strand Transfer Inhibitor
LTBI	Latent Tuberculosis Infection
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
P-gp	Permeability Glycoprotein
PHI	Protected health information
PK	Pharmacokinetics
QD	Once Daily
RPT	Rifapentine
SAE	Serious adverse event
SS	Steady State
TB	Tuberculosis
T_{max}	Time of maximum observable plasma concentration
UA	Urinalysis
β-hCG	Beta-Human Chorionic Gonadotropin

PROTOCOL SUMMARY

Synopsis	
Antiretroviral (ARV) drug therapy for persons living with human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) is multi-modal. The presence of HIV infection increases the risk of co-infection with tuberculosis which requires drug therapy using rifapentine (RPT) and isoniazid (INH). The combination of RPT/INH is well tolerated and is recommended as once-weekly therapy for a total of 12 weeks. RPT is an inducer of hepatic microsomal drug metabolizing P450 enzymes, which includes the cytochrome (CYP) 3A family of enzymes. Doravirine is a novel ARV for the treatment of HIV-1 infection. It is primarily metabolized by CYP3A. Co-administration of doravirine together with RPT may result in decreased doravirine exposure creating a potential for a drug-drug interaction when both drugs are used together. This study is designed to evaluate the pharmacokinetics of doravirine 100 mg given twice daily in the presence of RPT/INH, and to evaluate the safety and tolerability of doravirine when co-administered with RPT/INH in healthy volunteers.	
Overview of Study Design	
This is a phase I, open-label, two-period, fixed-sequence, drug interaction study to evaluate the effect of twice-daily doravirine co-administered with RPT and INH in healthy participants. All participants will receive doravirine alone for 4 days given twice daily during the first period. Doravirine dosing will resume from days 7-21. RPT and INH will be administered on days 7, 14, and 21 during the second period.	
Hypothesis	
When co-administered, once-weekly rifapentine will decrease the geometric mean concentrations of twice-daily doravirine by 15% compared to the geometric mean trough concentrations of twice-daily doravirine administered alone.	
Objectives and Endpoints	
Primary Objective	**Primary Endpoint**
Compare the change in plasma exposure-time profile, defined as $AUC_{(0\text{-last})}$, C_{max}, and C_{trough}, following multiple oral doses of twice-daily doravirine 100 mg co-administered with weight based, once-weekly RPT and INH.	Change in pharmacokinetic parameters measured as $AUC_{(0\text{-last})}$, C_{max}, and C_{trough}.
Secondary Objective	**Secondary Endpoint**

Evaluate the safety and tolerability of doravirine when co-administered with RPT and INH.	Proportion of subjects with treatment-emergent adverse events for safety parameters.

Study Population (Inclusion)

1. Healthy male or female between 18-60 years old at the time of screening.
2. Have a Body Mass Index (BMI) $\geq$ 19 and $\leq$ 33.
3. Weigh $\geq$ 45 kg but $\leq$ 120 kg.
4. Non-smoker (tobacco or electronic cigarettes).
5. Negative QuantiFERON-TB Gold at screening.
6. Subjects who agree to abstain from alcohol consumption throughout the duration of the study.
7. Female subjects of childbearing potential must demonstrate a urine beta-hCG consistent with non-pregnancy at the time of the screening visit and agree to the use (and/or have their partner use) an acceptable method of birth-control at initial screening, during the time of the trial and until four weeks after the last dose of drug following the last treatment period.
8. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.

Study Population (Exclusion)

1. History of clinically significant endocrine, gastrointestinal, cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary, dermatologic, psychiatricabnormalities or neurological (including stroke and chronic seizure) diseases.
2. >500 mL blood or plasma donation in the 6 weeks prior to study start.
3. Known anaphylactic or severe systemic reactions to any components of doravirine, rifapentine, isoniazid, or pyridoxine.
4. Positive HIV, Hepatitis B or Hepatitis C virus. Evidence of prior Hepatitis B infection and immunity is not exclusionary.
5. Latent or active tuberculosis infection. Documented prior fully treated latent tuberculosis is not exclusionary.
6. Females who are postpartum for < 12 months.
7. Current drug or alcohol abuse.
8. Received study drug in another study within 4 weeks or within 5 half-lives- which ever 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. Any clinical significant findings on lab, ECG, or physical exam at screening.
Compounds Under Investigation and Doses
Doravirine (Pifeltro) Class: Antiretroviral; Non-nucleoside reverse transcriptase inhibitor Availability: 100 mg oral tablet Investigational dosing: 100 mg orally twice-daily
Rifapentine (Priftin) Class: Anti-tuberculosis agent Availability: 150 mg oral tablet Investigational dosing: 32.1– 49.9 kg - 750 mg ≥50.0 kg - 900 mg (maximum)
Isoniazid Class: Anti-tuberculosis agent Availability: 100mg and 300 mg oral tablets Investigational dosing: 15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum
Number of Subjects
11

SCHEDULE OF EVENTS

Procedures (Screening – Study day 14)		Screening (Day -30)	Pre-study Day (Day -1)	Study Day 1	Study Day 2	Study Day 3	Study Day 4	Study Day 5	Study Day 6	Study Day 7	Study Day 8	Study Day 9	Study Day 10	Study Day 11	Study Day 12	Study Day 13	Study Day 14
Assessment of Eligibility		X															
Signed Consent Form		X															
Medical History		X															
Concomitant Medication Review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory	**Pregnancy Test**	X	X*						X							X	
	Complete Blood Count	X						X[d]			X[c]						
	Comprehensive Metabolic Panel	X						X[d]			X[c]						
	QuantiFERON-TB Gold	X															
	HIV, Hepatitis B & C	X															
	Alcohol & Drug Screen	X	X														
	Urinalysis	X															
Clinical Procedures	**Physical Exam¤**	X[a]		X			X		X[f]		X					X[f]	
	Vital Signs	X		X			X		X		X						X
	Electrocardiogram	X															
Research Labs	**Doravirine PK**			X[b]			X[b,c]	X	X	X[b]							
	Doravirine Trough																
Treatment	**Rifapentine (weight based)**									X[e]							X[e,f]
	Isoniazid (weight based)									X[e]							X[e,f]
	Pyridoxine 50 mg									X[e]							X[e]
	Doravirine 100 mg BID			X	X	X	X			X[e]	X	X	X	X	X	X	X
Assessment of Adverse Events			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inpatient			X	X	DC	X	X	X	X	DC						X	DC

Footnotes DC= Discharge from the Clinical Research Unit once all procedures are completed.

a. A height and weight measurement will be taken at screening.

b. A pre-doravirine PK will be taken prior to the AM dose.

c. PK sampling will begin following the end of the AM dose. The 12 hour time point will be taken prior to the PM dose. PK Sampling schedule can be found in section 6.4.2.2.

d. Safety labs will be drawn while the subjects are fasting prior to receiving doravirine.

e. Subjects will receive isoniazid on an empty stomach and receive breakfast approximately 1 hour following the isoniazid dose. Doravirine, rifapentine and pyridoxine will be given approximately 20 minutes after breakfast.

f. Subjects whose weight is $\leq$ 60 kg ($\leq$ 130 lbs) at screening will be reweighed the day prior to isoniazid and rifapentine doses to establish the correct dose (no other physical exam).

*Pregnancy test for women of childbearing potential
¤Physicals may be done the day prior except at the screening visit

Procedures (continued) (Study days 15 – Post-study)		Study Day 15	Study Day 16	Study Day 17	Study Day 18	Study Day 19	Study Day 20	Study Day 21	Study Day 22	Study Day 23	Study Day 24	Post-study Follow-up (+7 to 10 days)
Concomitant Medication Review		X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory	**Pregnancy Test***						X					
	Complete Blood Count	X[b]							X[b]			X
	Comprehensive Metabolic Panel	X[b]							X[b]			X
Clinical Procedures	**Physical Exam¤**	X					X[f]	X		X		X
	Vital Signs	X						X		X		X
Research Labs	**Doravirine PK**							X[a,c]	X	X	X	
	Doravirine Trough	X[c]	X[c]				X[d]					
Treatment	**Rifapentine (weight based)**							X[e]				
	Isoniazid (weight based)							X[e]				
	Pyridoxine 50 mg							X[e]				
	Doravirine 100 mg BID	X	X	X	X	X	X	X				
Assessment of Adverse Events		X	X	X	X	X	X	X	X	X	X	X
Inpatient							X	X	X	DC		

Footnotes

DC= Discharge from the Clinical Research Unit once all procedures are completed.

a. PK sampling will begin prior to the AM dose. The 12 hour time point will be taken prior to the PM dose of doravirine. PK sampling schedule can be found in section 6.4.3.2.

b. Safety labs will be drawn while the subjects are fasting prior to receiving doravirine.

c. Trough sampling will be prior to the AM dose.

d. Trough sampling will be prior to the PM dose.

e. Subjects will receive isoniazid on an empty stomach and receive breakfast approximately 1 hour following the isoniazid dose. Doravirine, rifapentine and pyridoxine will be given approximately 20 minutes after breakfast.

f. Subjects whose weight is $\leq$ 60 kg ($\leq$ 130 lbs) at screening will be reweighed the day prior to isoniazid and rifapentine doses to establish the correct dose (no other physical exam).

*Pregnancy test for women of childbearing potential

¤Physicals may be done the day prior except at the screening visit

1 INTRODUCTION

1.1 Background and Rationale

1.1.1 Background

Approximately 36.7 million people are living with Human Immunodeficiency Virus (HIV) worldwide with 21 million of those living with HIV receiving antiretroviral (ARV) drug therapy.[1] In those living with HIV, an estimated one-third of those individuals will be infected with *Mycobacterium tuberculosis*.[2] The presence of HIV infection increases the risk of co-infection with tuberculosis (TB) by 20 to 37-fold compared to HIV-uninfected individuals. An alarming 19-fold increase since 2004 in global persons co-infected with TB and HIV has shifted the focus to identifying detection and treatment gaps to reduce the incidence of active TB in those living with HIV and acquired immunodeficiency syndrome (AIDS).[3] In 2016, approximately 2 million persons globally were newly enrolled in HIV care. Approximately 42% of those 2 million persons living HIV initiated preventative treatment for TB reflecting the global increase in co-infection. As of 2016, approximately 85% of reported TB cases were on ARV therapy.[3]

Tuberculosis (TB) infection is caused by *Mycobacterium tuberculosis* complex. Transmission occurs through inhalation of the bacterium from an infected individual and may progress into active infection or persist in an inactive state. In the inactive state, host defenses contain the tuberculosis. Patients are asymptomatic and this is called latent TB (LTBI). However, reactivation of the disease may occur allowing transmission to others. In immunocompromised individuals, such as those living with HIV/AIDS, the risk of developing active TB disease following LTBI is high compared to those without HIV co-infection.[4,5] Following treatment for LTBI, the risk of progressing to active TB was reduced by as much as 62% in individuals co-infected with HIV.[6] Similar reports have also observed reduced transmission rates.[7] It is therefore critical to initiate treatment for LTBI in order to reduce progression to active TB disease and TB transmission in those living with HIV/AIDS.

The Centers for Disease Control and Prevention (CDC) currently recommends use of one of four possible LTBI treatment regimens consisting of the rifamycins, rifampin, rifabutin, and rifapentine (RPT), and isoniazid (INH).[8] INH and RPT given once-weekly under direct observational therapy for a duration of three months offers the shortest duration of treatment with comparable efficacy as the previous regimens.

Doravirine is a novel non-nucleoside reverse transcriptase inhibitor (NNRTI) currently approved in the United States for the treatment of HIV-1 infection in adult patients with no prior ARV treatment history. Doravirine is predominately metabolized by CYP3A4 with no clinically significant inhibition or induction of other cytochrome P450 enzymes.[9]

Doravirine is a substrate for the efflux transporter, permeability glycoprotein (P-gp), but does not inhibit P-gp. Doravirine is primarily metabolized by CYP3A and drugs that induce or inhibit CYP3A may affect the clearance of doravirine.

1.1.2 Mechanism of Interaction

The rifamycin family of antibiotics are notoriously known for potentiating DDIs through induction of cytochrome P450 drug metabolizing enzymes or drug transporters. The three currently US FDA marketed rifamycins include rifampin, rifabutin, and RPT.[10-12] The potency of induction is greatest with rifampin (100%) followed by RPT (85%) and rifabutin (40%).[13]

As such, clinically meaningful DDIs may present to therapeutically co-administered drugs who are CYP3A substrates. Enzyme induction may be time-dependent and variable depending on the TB regimen selected. In healthy volunteer studies, CYP3A4 induction was greatest when RPT was dosed daily compared to given every three days.[14]

DDI studies involving RPT dosed once-weekly together with ARV drugs have also shown time-dependent inductive effects compared to RPT dosed daily.[15,16]

1.1.3 Overview of Doravirine

1.1.3.1 Doravirine Clinical Experience in Healthy Volunteers

The safety and tolerability of doravirine were investigated in two single and multiple ascending dose studies that explored doses ranging from 6 to 1200 mg in healthy male subjects.[17] Doravirine was well tolerated at multiple doses of up to 750 mg once daily for up to 10 days. Headache, dizziness, nausea and fatigue were the most common reported adverse events related to the study drug. There were no clinically significant trends observed in laboratory assessments, vital signs or ECGs in healthy volunteers.

The pharmacokinetics of doravirine is expected to be similar between healthy subjects and HIV-1 infected subjects.

1.1.3.2 Doravirine Co-administered with Rifampin

When co-administered with multiple-doses of rifampin, peak and systemic exposures were reduced by 57% and 78%, respectively.[18] The parameter associated with virological suppressive efficacy, C_{24}, was reduced by 97%. Chronic administration of rifampin was therefore concluded to result in loss of efficacy overtime. As such, the regulatory labeling recommends against the co-administration of doravirine together with rifampin.

Doravirine was well tolerated administered alone or co-administered with rifampin. The most common adverse event was oropharyngeal pain reported in 2 subjects with all adverse events resolving by the end of study. There were no clinically meaningful changes observed in laboratory, vital signs or ECG in volunteers on doravirine co-administered with rifampin.[18]

1.1.3.3 Doravirine Co-administered with Rifabutin

Following multiple doses of rifabutin in healthy volunteers, doravirine exposures and C_{24} were observed to decrease by 50% and 68%, respectively.[19] Whereas the magnitude of induction from rifampin observed significant reductions in the exposure parameters, induction from rifabutin may be potentially mitigated using a dosing regimen consisting of doravirine 100 mg twice daily.

Doravirine was well tolerated when co-administered with rifabutin. The most commonly observed adverse events were headaches, pyrexia and chromaturia and was considered related to rifabutin treatment.[19]

1.1.4 Overview of Rifapentine

1.1.4.1 Rifapentine Clinical Experience in Healthy Volunteers

The 2018 update to the CDC recommendations for LTBI management have expanded the utility of once-weekly RPT to include those aged 2-17 years old.[20] RPT is approved by the FDA for the treatment of pulmonary TB caused by *Mycobacterium tuberculosis.*[10] RPT is standard of care and used extensively to manage LTBI or active TB infections. Doses of up to 20 mg/kg/day were well tolerated in healthy volunteers.[21]

The most common adverse events observed in healthy volunteers (n=7) at doses used in this study were constipation (29%), vomiting (14%), fever (14%), dizziness (14%), hyperbilirubinemia (14%), and lymphopenia (28%).[21]

1.1.5 Overview of Isoniazid

1.1.5.1 Isoniazid Clinical Experience in Healthy Volunteers

INH is the gold standard in the treatment of LTBI and active TB infection for both adult and children. In patients with LTBI, INH is either given alone for 6 or 9 months or together with rifamycins to shorten the duration of therapy. INH is approved by the FDA for the treatment of of all forms of tuberculosis in which organisms are susceptible.[22]

INH is safe and well tolerated in healthy volunteers from doses ranging from 300-900 mg.[23]

1.1.6 Overview of Pyridoxine

1.1.6.1 Pyridoxine Clinical Experience in Healthy Volunteers

Pyridoxine is an essential water soluble vitamin commonly sold over-the-counter as vitamin B_6.

1.2 Study Rationale

1.2.1 Rationale for Subject Population

The study will be conducted in healthy volunteers. The use of patient populations would be considered unethical based on the need to switch ARV regimens in those living with HIV to doravirine. Such practice would promote resistance and will be potentially exposing patients to

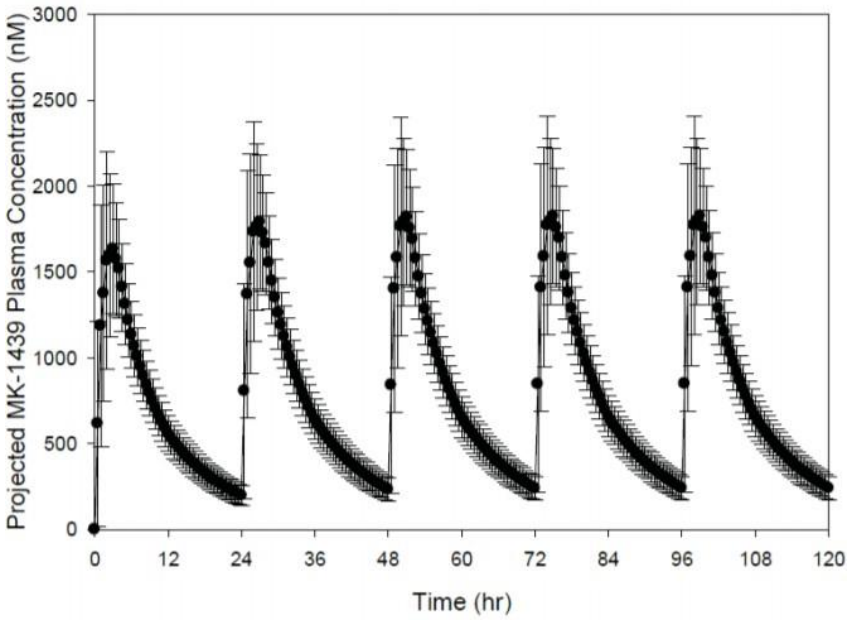
harm. Historically, this regimen has been studied in healthy volunteers in the presence of ARVs and is the common practice for conducting DDI studies.[14,15]

1.2.2 Rationale for Dose Selection

1.2.2.1 Doravirine

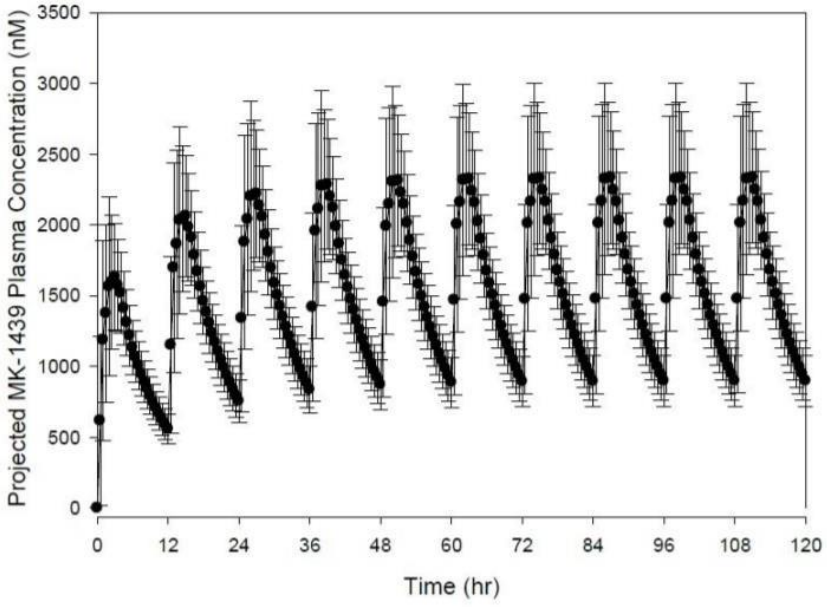
Doravirine 100 mg twice-daily dosing was based on simulated plasma concentration-time profiles following co-administration of once-daily 300 mg rifabutin in healthy volunteers (figure 1 and 2).

Figure 1. Simulated mean plasma concentration-time profiles of doravirine following administration of 100 mg once daily co-administered with 300 mg once-daily rifabutin in healthy volunteers.



Source: Doravirine FDA Clinical Pharmacology Review

Figure 2. Simulated mean plasma concentration-time profiles of doravirine following administration of 100 mg twice daily co-administered with 300 mg once-daily rifabutin in healthy volunteers.



Source: Doravirine FDA Clinical Pharmacology Review

Table 1 shows the mean plasma pharmacokinetic values following single oral doses of 100 mg doravirine with once-daily 300 mg rifabutin as the 100 mg regimen and 100 mg twice-daily regimen at day 1 and 5.

Table 1. Doravirine pharmacokinetic parameters as a once and twice-daily regimen in the presence of rifabutin.

Dose (mg)	Day	Ctrough (nM)	Cmax (nM)	AUC0-12 (uM*hr)	AUC0-24 (uM*hr)
100 mg QD DOR + 300 mg QD Rifabutin	1	189	1720	--	16.5
	5	230	1920	--	19.2
Fold Relative to 100 mg QD SS		.25	.85		.51
100 mg BID DOR + 300 mg QD Rifabutin	1	741†	2170	12.4	29.0
	5	881	2460	19.2	38.4
Fold Relative to 100 mg QD SS		.95	1.1		1.0

† Ctrough for BID dose at day 1 is C12. Other Ctrough data are C24.

Source: Doravirine FDA Clinical Pharmacology Review

Based on non-parametric superposition and simulation using 100 mg twice-daily doravirine co-administered with 300 mg once-daily rifabutin, a twice-daily 100 mg doravirine regimen achieves similar trough, AUC_{0-24} and C_{max} values as compared to a 100 mg once-daily dose of doravirine in the absence of an inducer.

It is with this evidence that a 100 mg twice-daily doravirine dose be selected to study the interacting effects when co-administered with RPT.

1.2.2.2 Rifapentine

The dose of RPT was selected based on the CDC recommended doses for LTBI. The recommended dose in adults is weight based, with a maximum dose of up to 900 mg weekly. The recommended dose based on the range of weights is:

- 32.1-50 kg: 750 mg
- >50 kg: 900 mg

1.2.2.3 Isoniazid

The dose of INH was selected based on the recommended doses for LTBI. The recommended dose in adults is weight based, with a maximum dose of up to 900 mg weekly. The recommended dose is 15 mg/kg.

1.2.2.4 Pyridoxine

The pyridoxine dose was selected based on the recommended doses for concurrent INH administration in LTBI. Pyridoxine is given to persons taking INH to reduce the risk of neuropathy. It is not anticipated that pyridoxine will impact the potential for DDI, it is safe and administered routinely with INH in clinical practice. The recommended dose is 50 mg daily.

1.3 Rationale for Endpoints

1.3.1 Pharmacokinetic Endpoints

Blood samples will be collected for doravirine PK analysis at pre-dose (0 hour), 0.5, 1, 1.5, 2, 3, 6, 12, 24, 36, 48 and 72 hours post dose on study days 4-7 (when doravirine is given alone) and 21-24 (following co-administration with RPT/INH). Doravirine trough concentrations will be taken on study days 15, 16, and 20.

The PK parameters prior to co-administration and following will be estimated using non-compartmental analysis. With patients on ARVs, drug concentrations determine efficacy (virological suppression). Therefore, the pharmacokinetic parameters associated with efficacy (C_{trough}, C_{max}, and AUC) will be compared prior to and following co-administration of RPT/INH.

1.3.2 Safety Endpoints

Safety for doravirine, INH, and RPT has been extensively studied and is well established. This study will observe the safety and tolerability of co-administration of doravirine, INH and RPT in

healthy volunteers. Given the extensive experience of all three 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 Objective

- Compare the change in plasma exposure-time profile, defined as $AUC_{(0\text{-last})}$, C_{max}, and C_{trough}, following multiple oral doses of twice-daily doravirine 100 mg co-administered with weight based, once-weekly RPT and INH in healthy HIV-negative adult volunteers.

2.1.2 Secondary Objective

- Evaluate the safety and tolerability of doravirine when co-administered with rifapentine and INH in healthy HIV-negative adult volunteers.

2.2 Endpoints

2.2.1 Primary Endpoints

- Change in the doravirine plasma exposure-time profile, as defined by $AUC_{(0\text{-last})}$, C_{max}, and C_{trough}.

2.2.2 Secondary Endpoints

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

3 STUDY DESIGN

This is a prospective, phase I, single-center, open-label, fixed-sequence, two-period, pharmacokinetic study investigating the effect of RPT and INH on the pharmacokinetics of doravirine.

Eleven healthy male or female adult subjects will be enrolled. Subjects will receive reference drug (doravirine 100 mg given as one 100 mg tablet twice-daily) for four study days during the first period. For the second period beginning on study day 7 (first week of perpetrator drug dosing), a weight-based dose of RPT/INH and pyridoxine 50 mg will be administered together with doravirine 100 mg twice daily.

Combination RPT/INH and pyridoxine 50 mg will be administered weekly (study days 14 and 21) while doravirine 100 mg will be dosed twice-daily from study day 7 onward to study day 21.

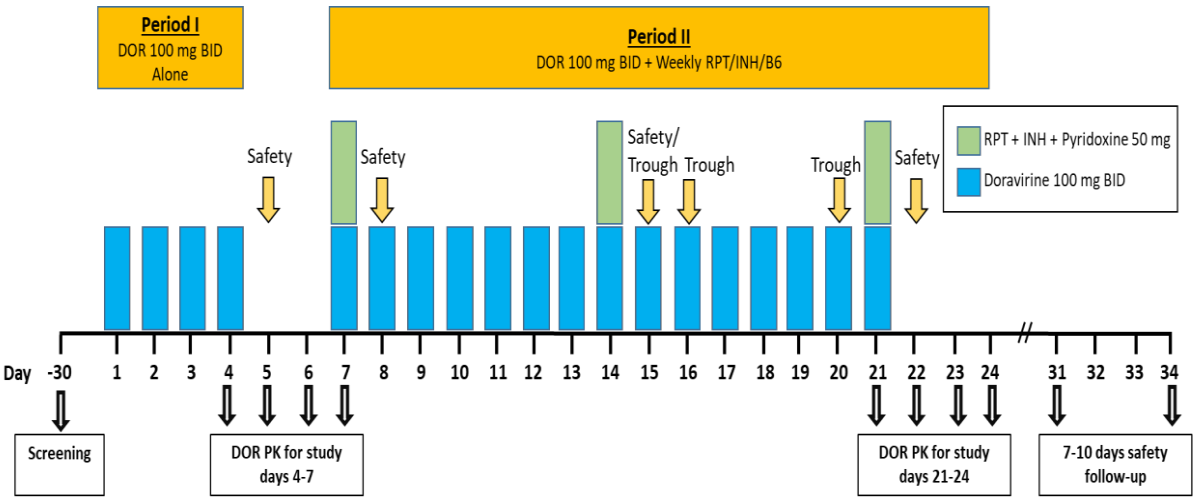


Figure 3: Dosing and sampling schedule.

4 HEALTHY VOLUNTEER SELECTION

4.1 Inclusion Criteria

Subject 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 male or female between 18-60 years old at the time of screening.
2. Have a Body Mass Index (BMI) $\geq$ 19 and $\leq$ 33.
3. Weigh $\geq$ 45 kg but $\leq$ 120 kg.
4. Non-smoker (tobacco or electronic cigarettes).
5. Negative QuantiFERON-TB Gold at screening.
6. Subjects who agree to abstain from alcohol consumption throughout the duration of the study.
7. Female subjects of childbearing potential must demonstrate a urine beta-hCG consistent with non-pregnancy at the time of the screening visit and agree to the use (and/or have their partner use) of an acceptable method of birth-control at initial screening, during the time of the trial, and until four weeks after the last dose of drug following the last treatment period.
8. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.

4.2 Exclusion Criteria

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

1. History of clinically significant endocrine, gastrointestinal, cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary, dermatologic, psychiatric abnormalities or neurological (including stroke and chronic seizure) diseases.
2. >500 mL blood or plasma donation in the 6 weeks prior to study start
3. Known anaphylactic or severe systemic reactions to any components of doravirine, rifapentine, isoniazid or pyridoxine.
4. Positive HIV, Hepatitis B or Hepatitis C virus. Evidence of prior Hepatitis B infection and immunity is not exclusionary.
5. Latent or active tuberculosis infection. Documented prior fully treated latent tuberculosis is not exclusionary.
6. Females who are postpartum < 12 months.
7. Current drug or alcohol abuse.
8. Received study drug in another study within 4 weeks or within 5 half-lives, which ever 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. Any clinical significant findings on lab, ECG or physical exam at screening.

4.3 Study Drug and Lifestyle Adherence

Enrolled subjects 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. Refrain from the use of alcohol and illicit drugs throughout the study duration
2. 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 subject

4.3.1 Outpatient Phone Contact

Subjects will be contacted by a CRU staff to ensure adherence to their evening doravirine doses.

4.3.2 Outpatient Adverse Event Reporting

CRU staff will assess for AEs during the outpatient phone calls.

4.4 Subject Discontinuation and Withdrawal

Subjects may withdraw consent at any time for any reason. In addition, a subject 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. Subjects who miss any treatment dose will be discontinued from the study at the discretion of the investigator. Any subject who

suffers a serious safety adverse events possibly- or probably-related-to study intervention will be discontinued.

4.5 Subject Replacement Strategy

If a subject discontinues from the trial, a replacement subject may be enrolled if deemed appropriate by the investigators. The replacement subject will generally receive the same treatment or treatment sequence (as appropriate) as the subject being replaced.

5 STUDY INTERVENTIONS

5.1 Treatment Drugs

The treatment drugs used in this study are doravirine, rifapentine, isoniazid, and pyridoxine. Table 2 highlights the dose, frequency, route of administration, and protocol regimen under investigation.

Table 2: Dose, frequency, route of administration, and protocol regimen under investigation

Drug	Dose	Dosage Form	Dosing Frequency	Route of Administration	Protocol Regimen
Doravirine	100 mg	Tablet	1 tablet twice daily	Oral	Twice daily administration on study days 1-4 and 7-21
Rifapentine	150 mg	Tablet	**Weight Based Once Weekly Dosing:** 32.1–49.9 kg - 750 mg (5 tablets) ≥50.0 kg - 900 mg (maximum – 6 tablets)	Oral	Once weekly administration on study days 7, 14, and 21
Isoniazid	300 mg	Tablet	**Weight Based Once Weekly Dosing:** 15 mg/kg rounded up to the nearest 50 or 100 mg (900 mg or 3 tablets maximum)	Oral	Once weekly administration on study days 7, 14, and 21
Pyridoxine	50 mg	Tablet	1 tablet once weekly	Oral	Once weekly administration on study days 7, 14, and 21

5.2 Treatment Allocation

Subjects will be screened using a screening number (SN) beginning consisting of an alpha-numeric code starting with SN 1001. Allocation numbers will begin with 201. Replacement subjects 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 subject safety. Trial procedures should be completed as close to the prescribed/scheduled time as possible.

6.2 Informed Consent

Consent must be documented by the subject'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 subject before participation in the trial. The subject will be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The informed consent will adhere to institutional review board (IRB) requirements, applicable laws and regulations.

6.3 Subject Recruitment and Screening

Within approximately 3 weeks prior to randomization, potential subjects will be evaluated to determine that they fulfill the entry requirements. Informed consent will be obtained from subjects who elect to participate in the study. Consent form must be signed before any study related procedures are done. Subjects will be asked to fast from food and drinks, except water, for at least 8 hours prior to the screening visit labs being drawn.

6.4 Study Visit Schedule

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

6.4.1 Study Day - 1

Subjects will be admitted to the CRU in the evening. Concomitant medications and adverse event assessments will be reviewed. A urine drug screen and serum alcohol will be obtained as well as pregnancy test for females of childbearing potential

6.4.2 Study Period 1- Pharmacokinetics of Doravirine Alone

Pharmacokinetic sampling windows are detailed in Appendix 1.

6.4.2.1 Period 1- Study Day 1

- Vital signs and physical exam pre-dose
- Pre-dose PK
- Administer one tablet of 100 mg doravirine orally twice daily with 240 mL of water; twice daily will be 12 hours apart (AM and PM dose)
- Assess for adverse events

6.4.2.2 Period 1- Study Days 2-7

- **Study Day 2:**
  - **Dosing (AM):** Subjects will be dosed with 100 mg doravirine in the AM with 240 mL of water
  - **Assessments (AM):** AEs and concomitant medication review.
  - **PK:** No PK taken
  - **Dosing (PM):** Subjects will be given their PM dose of 100 mg doravirine with 240 mL of water to take at home with instructions.
  - Subjects will be discharged from the CRU following all procedures

- **Study Day 3:**
  - **Dosing (AM):** Subjects will return to the CRU in the morning for their 100 mg doravirine AM dose
  - **Assessments (AM):** Subjects will be assessed for AEs and concomitant medications
  - **PK:** No PK
  - Subjects will be readmitted back to the CRU on the evening of study day 3
  - **Dosing (PM):** Subjects will be given their PM dose of 100 mg doravirine administered with 240 mL of water in the CRU
  - **Assessments (PM):** AEs and concomitant medications will be reviewed

- **Study day 4:**
  - **Assessments (AM):** Vital signs, AE, concomitant medications, physical exam, will be obtained pre-dose. Breakfast will be given pre-AM doravirine dose.
  - **DOSE (AM):** AM dose of 100mg Doravirine will be given with 240ml of water approximately 20mins after breakfast.
  - **PK:** A PK will be drawn prior to the AM dose of doravirine. Subsequent PK will be drawn at 0.5, 1, 1.5, 2, 3 and 6 hours post Day 4 AM dose.
  - **PK (PM):** A 12 hour post (Day 4 AM) dose PK will be drawn.
  - **Assessments (PM):** AEs
  - **Dose (PM):** Administer PM doravirine 100 mg dose with 240 mL of water.

- **Study day 5:**
  - **PK:** A 24 hour post (Day 4 AM) dose PK will be drawn.
  - **Dose:** No doravirine dosed.

- **Assessments:** AEs, concomitant medications and safety labs (CBC and CMP).
- **Study day 5 PK (PM):** A 36 hour post (Day 4 AM) dose PK will be drawn.

- **Study day 6:**
  - **PK:** A 48 hour post (Day 4 AM) dose PK will be drawn.
  - **Dose:** No doravirine dose.
  - **Assessments**: AEs and concomitant medications. Subjects ≤ 60kg will be weighed. See footnote f. page 11.
  - Discharge from the CRU on the morning of study day 6 after all procedures are completed.
  - Readmit subjects on the evening of study day 6. A Pregnancy test will be performed for women of childbearing potential.

- **Study day 7:**
  - **PK:** A 72 hour post (Day 4 AM) dose PK will be drawn.
  - **Assessments:** AEs, concomitant medications, and vital signs will be obtained for all subjects.
  - **Dose (AM):** Isoniazid 15mg/kg will be dosed orally on an empty stomach after the assessments above. Breakfast will be provided approximately 1 hour after isoniazid dose. Doravirine 100 mg, rifapentine (weight based) and pyridoxine 50 mg will be dosed orally approximately 20 minutes after breakfast with 240 mL of water.
  - Subjects will remain in the unit 2 hours post-dose to assess for any adverse reactions**.** Subjects will be discharged from the unit after 2 hours, however subjects may be kept longer per investigator discretion.
  - **Dosing (PM):** Subjects will be given their PM dose of 100 mg doravirine with 240 mL of water to take at home with instructions.

6.4.3 Study Period 2- Pharmacokinetics of Doravirine and Rifapentine and Isoniazid

Pharmacokinetic sampling windows are detailed in Appendix 1.

6.4.3.1 Period 2- Study Days 8-16

- **Study Days 8 – 16**
  - **Study day 8:**
    - Subjects will arrive to the CRU in the morning.
    - **Assessments:** Subjects will have a physical exam, vital signs and laboratory safety blood drawn (CBC and CMP)
    - **Dose (AM):** A 100 mg dose of doravirine will be given with 240 mL of water.
    - **Dosing (PM):** Subjects will be given their PM dose of 100 mg doravirine with 240 mL of water to take at home with instructions.

- **PK:** No PK

- **Study days 9-13**:
  - Subjects will arrive to the CRU each morning.
  - **Assessments:** AEs and concomitant medications will be assessed prior to AM doses each morning.
  - **Dose (AM):** A 100 mg dose of doravirine will be given with 240 mL of water. Subjects will be discharged after the procedures.
  - **Dosing (PM):** Subjects will be given their PM dose of 100 mg doravirine with 240 mL of water to take at home with instructions.
  - **PK:** No PK
  - **Study Day 13 PM**: Subjects will be admitted to the CRU. A pregnancy test will be performed for women of childbearing potential.
  - **Assessments**: AEs and concomitant medications. Subjects ≤ 60kg will be weighed. See footnote f. page 11.
  - **Dosing (PM)**: Subjects will be given their PM dose of 100 mg doravirine with 240 mL of water.
  - **PK**: No PK

- **Study day 14**:
  - **Assessments:** Subjects will have their vital signs taken and assessed for AEs and concomitant medications prior to AM dosing.
  - **Dose (AM):** Isoniazid 15 mg/kg will be dosed on an empty stomach after the procedures above. Breakfast will be provided approximately 1 hour after isoniazid dose. Doravirine 100 mg, rifapentine (weight based) and pyridoxine 50 mg will be dosed with 240 mL of water approximately 20 minutes after breakfast.
  - Subjects will remain in the unit 2 hours post-dose to assess for any adverse events. Subjects will be discharged from the unit after 2 hours, however subjects may be kept longer per investigator discretion
  - Subjects will be discharged following all procedures above
  - **Dosing (PM):** Subjects will be given their PM dose of 100 mg doravirine with 240 mL of water to take at home with instructions.
  - **PK:** No PK

- **Study day 15:**
  - Subjects will arrive to the CRU in the morning.
  - **Assessments**: AEs, concomitant medications, physical exam and safety lab draws (CBC & CMP) prior to AM dose.
  - **PK:** A doravirine trough level will be taken prior to the morning dose.

- **Dose (AM):** Doravirine 100 mg will be administered with 240 mL of water.
- **Dose (PM):** Subjects will be given their PM dose of 100 mg doravirine with 240 mL of water to take at home with instructions.

- **Study day 16:**
  - Subjects will arrive to the CRU in the morning
  - **Assessments**: AEs and concomitant medications.
  - **PK:** A doravirine trough level will be taken prior to the morning dose.
  - **Dose (AM):** Doravirine 100 mg will be administered with 240 mL of water
  - **Dose (PM):** Subjects will be given their PM dose of 100 mg doravirine with 240 mL of water to take at home with instructions.

6.4.3.2 Period 2- Study Days 17-24

Pharmacokinetic sampling windows are detailed in Appendix 1.

- **Study days 17-20:**
  - Subjects will arrive to the CRU in the morning
  - **Assessments:** AEs and concomitant medications
  - **PK:** No PK on study days 17 and 18
  - **<u>Study day 20:</u>**
    - **PK:** A doravirine trough level will be taken prior to the morning dose.
    - **Assessments:** Subjects <u>≤</u> 60kg will be weighed. See footnote f. page 11.
  - **Dose (AM):** Doravirine 100 mg will be administered with 240 mL of water.
  - Subjects will be admitted to the CRU on the evening of study day 20
  - **Assessments:** AEs and concomitant medications, a pregnancy test will be performed for women of childbearing potential.
  - **Dose (PM):** Administered PM doravirine 100 mg dose with 240 mL of water

- **Study day 21:**
  - **Assessments (AM):** Vital signs, AE, concomitant medications, physical exam will be obtained pre-dose.
  - **PK (Pre-dose):** A PK will be drawn prior to the AM dose of doravirine.
  - **Dose (AM):** Isoniazid 15 mg/kg will be dosed on an empty stomach after the procedures above. Breakfast will be provided approximately 1 hour after isoniazid dose. Doravirine 100 mg rifapentine (weight based) and pyridoxine 50 mg will be dosed with 240 mL of water approximately 20 minutes after breakfast
  - **PK (Post-dose):** Subsequent PK will be drawn at 0.5, 1, 1.5, 2, 3 and 6 hours post Day 21 AM dose.
  - **PK:** A 12 hour post (day 21 AM) dose PK will be drawn, prior to the Day 21 PM dose of doravirine.

- **Assessments (PM):** AEs
- **Dose (PM):** Administer PM doravirine 100 mg dose with 240 mL of water

- **Study day 22 PK:**
  - **Assessments:** AEs, concomitant medications and safety laboratories (CBC & CMP)
  - **PK (AM):** A 24 hour post (day 21 AM) dose PK will be drawn.
  - **Dose:** No dose of doravirine given
  - **PM (PM):** A 36 hour post (day 21 AM) dose PK will be drawn.

- **Study day 23 PK:**
  - **Assessments:** AEs, concomitant medications, physical exam and vital signs
  - **PK:** A 48 hour post (day 21 AM) dose PK will be drawn.
  - **Dose:** No dose of doravirine given
  - Subjects will be discharged from the CRU following the procedures

- **Study day 24 PK:**
  Subjects will arrive at the CRU in the morning.
  - **Assessments:** AEs and concomitant medications
  - **PK:** A 72 hour post (day 21 AM) dose PK will be drawn.
  - **Dose:** No dose of doravirine given
  - Subjects will be discharged from the CRU following the procedures

NOTE: Subjects will be given a reminder phone call ± 30 minutes of their scheduled dose time for all at home PM doses of doravirine.

6.4.4 Post-Study Follow-up – Approximately 7-10 days after the last dose of doravirine.

- Subjects will be required to follow up post study to assess for adverse events and safety
- Safety labs will be drawn followed by a physical exam and vital signs. Comparisons will be drawn to pre-study.

6.5 Domiciling

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

6.6 Clinical Procedures & Assessments

6.6.1 Medical History

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

6.6.2 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.

6.6.3 12-Lead Electrocardiogram

Subjects remain supine for at least 2 minutes prior to collection of ECG.

6.6.4 Vital Signs

Subjects 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. All methods of measurement (oral or tympanic) should be consistent for all subjects throughout the study.

6.6.5 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 must review the laboratory report, document review on lab report, and record any clinically significant abnormal findings occurring during the study that meet the reporting requirements in the AE section of the CRF. The laboratory reports must be filed with the source documents.
- 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.

6.6.6 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 subject 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.

6.7 Study Restrictions

6.7.1 Diet, Fruit, and Medications Restrictions

Subjects must fast from food and drinks with the exception of water for 8 hours prior to the screening visit, Day 5, Day 8 , Day 15 and the follow up visit for laboratory safety tests. Subjects will also fast for 8 hours prior and approximately 1 hour after the Isoniazid doses on day 7, 14, 21. Subjects will 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.

6.7.2 Alcohol Restriction

Alcohol consumption must be avoided throughout the entirety of the study until after the post-study visit. Additional alcohol tests may be performed at the judgment of the investigator if a there is reason to believe a subject has consumed alcohol.

6.7.3 Smoking Restriction

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

6.7.4 Activity Restrictions

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

6.8 Contraception and Pregnancy Testing

Women of childbearing potential can be enrolled. However, two (2) acceptable methods of contraception must be used beginning at the screening visit, throughout the trial (including washout period) and until 4 weeks after the last dose of trial drugs in the last treatment period. Acceptable methods of birth control are two (2) of the following: intrauterine device (IUD with or without local hormone release), implantable hormonal contraceptives (e.g. etonogestrel implant), diaphragm, spermicides, cervical cap, contraceptive sponge, and/or condoms. Abstinence is an alternative life style and subjects practicing abstinence may be included in the trial. Hormonal oral contraceptives are not allowed as a method of birth control in this trial.

Female subjects of childbearing potential will be tested for urine β-human chorionic gonadotropin (hCG) at Screening and day -1. In the case of a positive urine β-hCG pregnancy test at Screening or day -1, the subject will not be enrolled in the trial. Female subjects with a positive urine β-hCG pregnancy test during the study (as identified on either study days 6, 13, and 20) will be discontinued from the study.

6.9 Subject Identification Card

All subjects will be given a Subject 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 subject with a Subject Identification Card after the subject provides written informed consent.

6.10 Standardized Meals

Meals (Breakfast, lunch, dinner and snacks) will be provided to subjects during the admission days.

6.11 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 subjects. 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 subject during his/her participation in the entire study.

6.12 Study Stopping Rules

The safety profile for isoniazid and rifapentine have been well established in combination. Doravirine safety has been described for the administration with other rifamycins (rifampin and rifabutin), without significant identification of safety signal. An independent safety physician will review all serious adverse events.

- **If there is a serious adverse event, possibly- or probably- related to the study intervention, the independent safety monitor will determine if the study will be permanently stopped, halted, and subsequently restarted.**

- **If there are two serious adverse event, possibly- or probably- related to the study intervention, the study will be stopped.**

- **Individual subjects who develop an AST or ALT of $\geq$ 2.5 x the upper limit of normal or become pregnant during the study will be discontinued from the study.**

7 DRUG SUPPLY

The Thomas Jefferson University Investigational Drug Service Pharmacy will be responsible for maintaining appropriate records and ensure appropriate supply, handling, storage, distribution and usage of these materials in accordance with the protocol and applicable laws and regulations.

Doravirine will be supplied by Merck & Co., Inc. Rifapentine, isoniazid, and pyridoxine will be purchased through the Thomas Jefferson University Hospital Pharmacy.

8 POTENTIAL RISKS AND BENEFITS

8.1 Potential Risks Associated with Doravirine

The following most common adverse events (for All Grades) have been reported (≥ 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 + lamivudine + tenofovir disoproxil: 4%)
    - Defined as: altered state of consciousness, lethargy, somnolence, syncope
  - Sleep disorders and disturbances (Doravirine + + tenofovir disoproxil: 12%)
    - Defined as: abnormal dreams, hyposomnia, initial insomnia, insomnia, nightmare, sleep disorder, somnambulism
  - Dizziness (Doravirine + tenofovir disoproxil: 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% have been reported with chronic use of doravirine in patients with HIV on concomitant ARVs.

- **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%)
  - Asparate 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%)

8.2 Potential Risks Associated with Rifapentine

Potential risks and adverse events are derived from studies in patients with active pulmonary tuberculosis and LTBI. In patients treated for active pulmonary tuberculosis, therapy consisted of an initial 2 month therapy of RPT twice weekly co-administered with INH, pyrazinamide and ethambutol. A continuation phase followed where RPT was administered once weekly together with INH for 120 days. As such, the reported adverse event rates may be due to other medications given along with RPT and prolonged exposure. Although possible, the adverse event profile in this study protocol will be expected to be less than those observed in clinical trials.

Treatment emergent adverse events occurring in ≥5% of patients during the continuation phase (RPT once weekly) include[10]:

- **Hematologic**
  - Neutropenia (8.5%)

Less commonly observed adverse events occurring in <5% of patients during the continuation phase (RPT once weekly) include:

- **Hematologic**
  - Anemia (1.6%)
  - Lymphopenia (3.2%)

- Leukocytosis (1.6%)
- Thrombocytosis (0.3%)
- Thrombocytopenia (1.3%)
- Non-protein nitrogen increase (3.2%)

- **Eye**
  - Conjunctivitis (0.3%)
- **Gastrointestinal**
  - Dyspepsia (1.3%)
  - Vomiting (0.9%)
  - Nausea (0.6%)
  - Diarrhea (0.6%)
- **General**
  - Back pain (3.5%)
  - Abdominal pain (1.3%)
  - Fever (0.3%)
  - Anorexia (2.5%)
- **Hepatic & Biliary**
  - Hepatitis (RPT/INH in LTBI: 0.6%)
  - ALT increase (2.2%)
  - AST increase (2.2%)
- **Musculoskeletal**
  - Arthralgia (0.9%)
- **Neurologic**
  - Headache (0.9%)
  - Dizziness (0.3%)
- **Respiratory**
  - Hemoptysis (1.9%)
  - Coughing (2.8%)
- **Dermatologic**
  - Rash (2.5%)
  - Sweating increase (2.6%)
  - Pruritus (0.9%)

8.3 Potential Risks Associated with Isoniazid

Potential risks and adverse events were derived from patient populations. The most frequent reactions are those affecting the nervous system and the liver. The most common adverse event (>10%) observed in patients were increase in serum transaminases consistent with the signs and symptoms of acute hepatitis.[22] In most instances, enzyme levels return to normal and generally, there is no necessity to discontinue medication during the period of mild serum

transaminase elevation. There is a higher frequency of INH associated hepatitis among those who are aged greater 35 years old, daily users of alcohol, chronic alcohol users, and black and Hispanic women. The CDC recommends clinical observation and not lab monitoring. In this study labs will be monitored which will be a sensitive detection of liver enzyme elevation.

Nervous system reactions, particularly peripheral neuropathy, is the most common toxic effect and is dose-related. The risk is higher in those who are malnourished, alcoholics, and diabetics, none of whom will be enrolled in this study. Pyridoxine repletion is recommended to prevent the risk of peripheral neuropathy.

Aside from nervous system and hepatic reactions, other adverse events include (frequency not provided):

- **Gastrointestinal**
  - Nausea, vomiting, epigastric distress, and pancreatitis
- **Hematologic**
  - Agranulocytosis; hemolytic, sideroblastic or aplastic anemia, thrombocytopenia; and eosinophilia
- **Hypersensitivity**
  - Fever, skin eruptions (morbilliform, maculopapular, purpuric or exfoliative), lymphadenopathy, vasculitis, toxic epidermal necrolysis, and drug reaction with eosinophilia syndrome (DRESS)
- **Metabolic and Endocrine**
  - Pyridoxine deficiency, pellagra, hyperglycemia, metabolic acidosis and gynecomastia
- **Miscellaneous**
  - Rheumatic syndrome and systemic lupus erythematosus-like syndrome

8.4 Potential Risks Associated with Pyridoxine

Pyridoxine is a water soluble vitamin that is naturally present in foods and available as a dietary supplement. Potential risks with pyridoxine were derived from population studies and case reports.[24] Pyridoxine is virtually safe and commonly consumed, however high intakes of 1-6 grams for 12-40 months can cause severe and progressive sensory neuropathy.[25] The adverse effect profile is expected to be negligible in our protocol with the use of 50 mg weekly for 3 weeks.

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

9.1 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.

9.1.1 Adverse Event (AE)

An adverse event is defined as any untoward medical occurrence in a subject 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 subject is enrolled into the study until the post-trial visit. At each contact with the subject, 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.

9.1.2 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.

9.2 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 subject'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 subject 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 subject 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)
- Subject number

9.3 Data Safety Monitoring Plan (DSMP)

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. An independent Medical Monitor will be assigned to this study. The medical monitor will be a physician who is not directly involved in the study and is not currently collaborating with the sponsor/investigator on any other trial and who has a working knowledge of the drugs involved in this study. 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.

10 DATA COLLECTION, STUDY MONITORING, AND RECORD MANAGEMENT

10.1 Data Collection and Reporting

Data for this study will be collected using eCRFs. The investigator and study site staff will receive system documentation, training, and support for the use of the eCRF. Visit-specific data should be entered into the eCRF and be ready for review as soon as possible, but no later than 5 days after each visit/time point. All protocol-required information collected during the study must be entered by the investigator or designated representative in the source documents and eCRF. All data entry, modification, or deletion will be recorded automatically in an electronic audit trail indicating the individual subject, original value, the new value, the reason for change, who made the change, and when the change was made. All data changes will be clearly indicated with a means to locate prior values. The system will be secured to prevent unauthorized access to the data or the system. This will include the requirement for a user ID and password to enter or change data. The investigator will maintain a list of individuals who are authorized to enter or correct data and their system ID. The investigator or designated sub-investigator, following review of the data in the eCRF, will confirm the validity of each subject's data by electronic signature.

10.2 Study Monitoring

Study progress will be monitored by the sponsor or its representative as frequently as necessary to ensure adequate and accurate data collection, protocol compliance, and study conduct in accordance with accepted regulatory requirements. The principal investigator must make all the subject data available to the monitor for review during the planned site monitoring visits. Arrangements for monitoring visits will be made in advance, except in emergency cases.

10.3 Investigator Study Files

The principal investigator is responsible for maintaining all study-related documents in study files. The sponsor will notify the principal investigator when retention of study files is no longer necessary. The study will be compliant with CFR 21 312.62 and 312.57.

10.4 Retention of Records

Standard protocol is that essential documents should be retained until at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications, or at least 2 years have elapsed since the formal discontinuation of the investigational product. For this investigator initiated trial, records will be stored in a secure location until all anticipated publications stemming from study conduct are completed.

11 STATISTICAL AND PHARMACOKINETIC METHODS

11.1 Sample Size Estimation

Sample size was calculated from the published variability on doravirine 200 mg trough concentrations in HIV-infected subjects following multiple doses (Geometric mean = 964 nmol/L; 95% CI: 694 – 1340).[26] Using a significance level of 5% with a two-sided paired t-test, a sample size of 11 provided greater than 80% power to detect a change of 15% in doravirine (paired log-mean 6.87 versus 6.71) trough concentrations.

The standard deviation of the paired difference was calculated assuming independence between the reference (doravirine alone) and co-administrated doravirine and rifapentine/isoniazid. The standard deviation of the paired difference was assumed to be 0.12 for both the reference and the RPT/INH co-administered with doravirine group.

11.2 Pharmacokinetic Analysis

Plasma concentrations of doravirine will be used to calculate the pharmacokinetic parameters for each subject in the presence or absence of multiple doses of RPT/INH. Analysis for the primary pharmacokinetic objective 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 12 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 subject. 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 AUC0-last, C_{max} and C_{trough}

Doravirine pharmacokinetic parameter estimates computed before and after RPT/INH exposure will be compared using a paired student's t-test. Statistical significance will be defined as a p-value <0.05. Geometric mean ratios and 90% confidence intervals will be calculated for RPT/INH and doravirine administrations (i.e. RPT/INH co-administered with multiple-dose 100 mg twice-daily doravirine compared to a multiple-dose doravirine 100 mg twice-daily alone).

Results for the primary pharmacokinetic objective will be reported in summary tables and figures. Subject demographics and treatment related adverse events will be summarized and tabulated.

11.3 Safety Analysis

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

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

12 SUPPORTING DOCUMENTATION

12.1 Appendix 1: Time Windows for Serial Assessments & Dosing

Sampling Window

Sampling Timepoint (Hours)	Sampling Window (Minutes)
Pre-dose (doravirine) on study day 1	-120 minutes to 0 hour
0 hour (Pre-dose)	-10 minutes to +10 minutes
> 0 hour – 4 hours	-10 minutes to +10 minutes
> 4 hours – 24 hours	-10 minutes to +10 minutes
> 24 hours – 72 hours	-15 minutes to +15 minutes
Trough concentrations	-30 minutes to +30 minutes

Dosing Window

Dosing Timepoint (Hours)	Dosing Window (Minutes)
(doravirine) on study day 1 AM dose	0 hour
All other doses	+/- 30 minutes from actual 0 hour time

12.2 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 safety and other laboratory assessments.

Laboratory Assessment	**Parameter**
Hematology	▪ Platelet count ▪ Hemoglobin ▪ Hematocrit ▪ WBC with differential ▪ Partial thromboplastin time ▪ Prothrombin time
Chemistry	▪ Albumin ▪ Calcium ▪ Chloride ▪ Bicarbonate ▪ 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	▪ Follicle Stimulating Hormone (FSH) ▪ Urine β human chorionic gonadotropin (β hCG) ▪ 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 ▪ QuantiFERON-TB Gold Tuberculosis screen

	▪ Urine drug screen to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines ▪ Blood alcohol level

12.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting

12.3.1 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

12.3.2 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

12.3.3 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

12.3.4 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 ETHICS AND PROTECTION OF HUMAN SUBJECTS

13.1 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.

13.2 Informed Consent

The ICH Tripartite Guideline for Good Clinical Practice establishes the general requirements for informed consent. Each subject 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 subject must consent in writing to study participation. The subject 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 subject. Each subject will receive a copy of his or her signed ICF.

13.1 Subject 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.

14 SUPPLEMENTAL MATERIALS

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.

- Case Report Forms
- Biospecimen sample chain of custody forms, shipment
- Source Documents
- Laboratory and Specimen Handling Manual
- Pharmacy Manual
- Data Management Plan
- Pharmacokinetic Analysis Plan
- DSMP

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