CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1, Open-label, Multicohort Study to Evaluate the Impact of Inhibitors and Inducers of Cytochrome P450 Enzyme (CYP)3A and/or P-glycoprotein (P-gp) on the Pharmacokinetics (PK) of Vesatolimod (VES) in Virologically Suppressed Adults With HIV-1 on Antiretroviral Therapy (ART)
Short Title:	Drug-Drug Interaction Study of Vesatolimod in Adults With HIV-1 Who Have Very Low or Undetectable Virus Levels
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
IND Number:	122452
EudraCT Number:	Not Applicable
ClinicalTrials.gov Identifier:	NCT05458102
Indication:	Human immunodeficiency virus type 1 (HIV-1) infection
Protocol ID:	GS-US-382-1587
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Original: 25 March 2022 Amendment 1: 05 May 2022 Amendment 2: 28 June 2022 Amendment 3: 12 December 2022

This study will be conducted under United States Food and Drug Administration investigational new drug application regulations (21 Code of Federal Regulations Part 312).
This study will be conducted in compliance with this protocol and in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

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GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the log concentration of drug versus time curve of the drug
$\%AUC_{exp}$	percentage of AUC extrapolated between AUC_{last} and AUC_{inf}
3TC	lamivudine
ABC	abacavir
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
APR	Antiretroviral Pregnancy Registry
ART	antiretroviral therapy
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC_{inf}	area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$
AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
BCRP	breast cancer resistance protein
BIC	bictegravir
BMI	body mass index
BSA	body surface area
bNAbs	broadly neutralizing antibodies
CD	clusters of differentiation
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
CL/F	apparent oral clearance
C_{last}	last observed quantifiable concentration of the drug
CL_{cr}	creatinine clearance
C_{max}	maximum observed concentration of drug
COBI	cobicistat
COVID-19	coronavirus disease 2019
CRF	case report form
CRS	cytokine release syndrome
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450 enzyme
DNA	deoxyribonucleic acid
DOR	doravirine
DTG	dolutegravir
ECG	electrocardiogram

eCRF	electronic case report form
EDC	electronic data capture
ET	early termination
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Gilead	Gilead Sciences/Gilead Sciences, Inc.
GLSM	geometric least-squares mean
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IFN	interferon
IFN-α	interferon-alpha
IL	interleukin
IND	investigational new drug
IRB	institutional review board
ISG	interferon-stimulated gene
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger RNA
NRTI	nucleoside reverse transcriptase inhibitor
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
PBPK	physiologically based pharmacokinetics
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
pDC	plasmacytoid dendritic cell
P-gp	P-glycoprotein
PI	principal investigator
PK	pharmacokinetic(s)
PR (interval)	electrocardiographic interval occurring between the onset of the P wave and the QRS complex representing time for atrial and ventricular depolarization, respectively
PS	Patient Safety
PT	preferred term
PWH	people with HIV-1

QRS	electrocardiographic deflection between the beginning of the Q wave and termination of the S wave, representing time for ventricular depolarization
QT (interval)	electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using the Fridericia formula
RAL	raltegravir
RFB	rifabutin
RMD	recommended maintenance dose
RNA	ribonucleic acid
SAE	serious adverse event
SOC	system organ class
SRT	safety review team
SSR	special situation report
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
T_{last}	time (observed time point) of C_{last}
TLR7	toll-like receptor 7
T_{max}	time (observed time point) of C_{max}
ULN	upper limit of normal
UNAIDS	United Nations Programme on HIV/AIDS
US, USA	United States, United States of America
USPI	United States Prescribing Information
VES	vesatolimod
VOR	voriconazole
V_z/F	apparent volume of distribution of the drug

PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Study Title: A Phase 1, Open-label, Multicohort Study to Evaluate the Impact of Inhibitors and Inducers of Cytochrome P450 Enzyme (CYP)3A and/or P-glycoprotein (P-gp) on the Pharmacokinetics (PK) of Vesatolimod (VES) in Virologically Suppressed Adults With HIV-1 on Antiretroviral Therapy (ART)

Short Title: Drug-Drug Interaction Study of Vesatolimod in Adults With HIV-1 Who Have Very Low or Undetectable Virus Levels

IND Number: 122452
EudraCT Number: Not Applicable
Clinical Trials.gov Identifier: NCT05458102

Study Centers Planned: Multiple centers in the United States

Objectives and Endpoints:

Primary Objective(s)	Primary Endpoint(s)
To evaluate the impact of the following drugs on vesatolimod (VES) pharmacokinetics (PK) • Cobicistat (P-glycoprotein [P-gp], breast cancer resistance protein [BCRP], and strong cytochrome P450 enzyme [CYP]3A inhibitor) • Voriconazole (strong CYP3A inhibitor) • Rifabutin (moderate CYP3A inducer) To evaluate the safety of VES administered alone and in combination with inhibitors and inducers of metabolizing enzymes and transporters involved in VES disposition	Primary PK parameters throughout the study • VES AUC_{last}, AUC_{inf}, C_{max} Secondary PK parameters throughout the study • VES $\%AUC_{exp}$, T_{max}, C_{last}, T_{last}, λ_z, $t_{1/2}$, CL/F, V_z/F Safety parameters • Incidence of treatment-emergent adverse events (TEAEs) and laboratory abnormalities throughout the study
CCI [redacted]	CCI [redacted]
CCI [redacted]	[redacted]

Study Design: This is an open-label, multicohort Phase 1 study to evaluate the impact of inhibitors and inducers of CYP3A and/or P-gp on the PK and PD of VES in virologically suppressed adults with HIV-1 on antiretroviral therapy (ART). The overall study design is shown in Figure 1.

The study will be conducted in 2 cohorts:

- Cohort 1: An open-label, single sequence cohort to evaluate the impact of cobicistat (COBI; P-gp, BCRP, and strong CYP3A inhibitor) and voriconazole (VOR; strong CYP3A inhibitor) on VES PK and PD
- Cohort 2: An open-label, single sequence cohort to evaluate the impact of rifabutin (RFB; moderate CYP3A inducer) on VES PK and PD

A safety review team will assess relevant and available safety data for the first 3 participants in Cohort 1 who are dosed with COBI (up to and including Period 2 Day 3) before initiation of any additional participants in Cohort 1.

Number of Participants Planned: Approximately 45 enrolled: 25 in Cohort 1 and 20 in Cohort 2.

Target Population: Male and nonpregnant, nonlactating female, HIV-1 infected, virologically suppressed adults on ART

Duration of Dosing:

Cohort 1: VES will be administered as a single dose in Periods 1, 2, and 3; COBI will be administered for 5 days in Period 2; and VOR will be administered for 6 days in Period 3.

Cohort 2: VES will be administered as a single dose in Periods 1 and 2; and RFB will be administered for 9 days in Period 2.

Study Duration:

Cohort 1: Approximately 55 days (not including the 35-day screening window)

Cohort 2: Approximately 35 days (not including the 35-day screening window)

Diagnosis and Main Eligibility Criteria:

Eligible participants will be adults with HIV-1 assigned male at birth or nonpregnant, nonlactating participants assigned female at birth aged at least 18 years, on an ART regimen for at least 6 consecutive months, with no change in the ART regimen within 2 months prior to screening, and with documented plasma HIV-1 RNA levels less than 50 copies/mL at screening and for at least 6 months preceding the screening visit (using all available viral load measurements), and a CD4 T cell count of greater than or equal to 350 cells/μL. Participants' ART will be consistent with the protocol requirements and participants will not receive prohibited medications from 14 days prior to study drug dosing through the follow-up visit. In addition, participants will be negative for chronic hepatitis B virus (HBV) infection (defined as positive hepatitis B surface antigen [HBsAg] and/or positive hepatitis B core antibody with positive reflex HBV DNA polymerase chain reaction [PCR] [Note: positive HBV core

antibody with negative reflex HBV DNA PCR results are acceptable]) and active hepatitis C virus (HCV) infection (defined as positive hepatitis C antibody and HCV RNA above lower limit of quantification [Note: positive anti-HCV antibody and negative HCV PCR results are acceptable]) and will be in good general health as determined by the investigator at the screening evaluation performed no more than 35 days prior to the scheduled first dose.

Study Procedures/Frequency:

Following completion of screening and admission assessments, eligible participants will receive the following treatments:

- Cohort 1:
  - In Period 1, participants will receive a single dose of VES 2 mg on Day 1.
  - In Period 2, participants will receive COBI 150 mg once daily on Days 1 to 5; a single dose of VES 2 mg will be coadministered on Day 2.
  - In Period 3, participants will receive a loading dose of VOR 400 mg twice daily on Day 1, then VOR 200 mg twice daily on Days 2 to 6; a single dose of VES 2 mg will be coadministered in the morning on Day 3.

  There will be a washout period of 7 to 14 days between treatments in Period 1 Day 1 and Period 2 Day 1 and a washout period of 14 to 21 days between treatments in Period 2 Day 5 and Period 3 Day 1. Participants should inform the site of any adverse event (AE) during the washout period.
- Cohort 2:
  - In Period 1, participants will receive a single dose of VES 6 mg on Day 1.
  - In Period 2, participants will receive RFB 300 mg once daily on Days 1 to 9; a single dose of VES 6 mg will be coadministered on Day 6.

  There will be a washout period of 7 to 14 days between treatments in Period 1 Day 1 and Period 2 Day 1. Participants should inform the site of any AE during the washout period.
  - Note: Participants in Cohort 2 will be on a dolutegravir-based ART regimen

Vesatolimod is provided as 2 mg tablets, COBI is provided as 150 mg tablets, VOR is provided as 200 mg tablets, and RFB is provided as 150 mg capsules.

Clinic Confinement/Follow-Up

Following screening and admission assessments, eligible participants will be confined to the study center as follows:

- Cohort 1
  - In Period 1, participants will be confined beginning Day −1 until completion of assessments on Day 2
  - In Period 2, participants will be confined beginning on Day −1 until completion of assessments on Day 3
  - In Period 3, participants will be confined beginning on Day −1 until completion of assessments on Day 4

- Cohort 2
  - In Period 1, participants will be confined beginning on Day −1 until completion of assessments on Day 2
  - In Period 2, participants will be confined beginning on Day −1 until completion of assessments on Day 7

Participants may remain confined for a longer duration within each treatment period if this is preferred by the principal investigator.

If a participant is experiencing signs and symptoms of cytokine release syndrome (CRS; see toxicity management below), the participant will remain confined (for CRS symptoms of Grade 1) or immediately be transferred to a hospital or emergency department (for CRS symptoms of ≥ Grade 2) until symptoms resolve.

Participants will return 10 ± 3 days after the last dose of VES for an in-clinic follow-up visit.

Study Drug Administration

All study treatments will be administered orally at approximately the same time relative to VES dosing in each period (± 1 hour) each day with 240 mL of water. All VES doses will be administered in the morning following an overnight fast (no food or drinks except water) for at least 8 hours. Participants will continue to fast until after collection of the 4-hour PK sample, relative to VES dosing. Additionally, participants will be restricted from water consumption from 2 hours before through 2 hours after VES dosing, except for the 240 mL given with the study drug. All COBI, VOR, and RFB doses will be administered on an empty stomach, defined as no food or drinks, except water, for at least 2 hours before and 2 hours after dosing.

Pharmacokinetic Assessments

Plasma PK:

Plasma samples for quantification of VES concentrations will be collected at the following time points relative to VES dosing in each period:

- Predose (within 0.5 hours before dosing) and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 48, 72, and 96 hours postdose

Plasma concentrations of COBI, VOR, and RFB may be determined and PK parameters may be estimated.

Time windows allowed for PK samples to be collected are provided in Table 8.

Clinical staff should make every effort to ensure that the sampling time is as close as possible to the nominal time. The exact time and date of the blood draw must be recorded in the electronic data capture (EDC) system.

Biomarker Testing

Biomarker samples will be collected to assess the PD and safety following VES administration.

Serum samples for biomarker assessments will be collected at the following time points relative to VES dosing in each period:

- Predose (within 0.5 hours before dosing) and 4, 8, 12, 24, 48, and 96 hours postdose

The serum biomarkers to be evaluated may include (but not limited to): interferon-alpha (IFN-α), interleukin (IL)-1 receptor antagonist, interferon gamma inducible protein-10, interferon-inducible T cell alpha chemoattractant, interferon-gamma, IL-1 beta, IL-6, tumor necrosis factor alpha, and C-reactive protein.

Whole blood samples for ISG mRNA expression (including, but not limited to, MX1, ISG15, OAS1) will be collected at the following time points relative to VES dosing in each period:

- Predose (within 0.5 hours before dosing) and 8, 12, 24, 48, 72, and 96 hours postdose

Whole blood for immune cell phenotyping will be collected at the following time points relative to VES dosing in each period:

- Predose (within 0.5 hours before dosing) and 24, 72, and 96 hours postdose

Whole blood to evaluate VES TruCulture cytokine response will be collected for Cohort 2 at the following visit in Period 1:

- On Day 1 (predose)

A time window of ± 10% will be allowed for biomarker samples collected through 8 hours postdose. Biomarker samples collected beyond 8 hours postdose will have a ± 30-minute window.

Clinical staff should make every effort to ensure that the sampling time is as close as possible to the nominal time. The exact time and date of the blood draw must be recorded in the EDC system.

Pharmacogenetic Assessments

A pharmacogenetics (PGx) sample will be collected on Day 1 Period 1 if applicable (preferably) or at any other time during the study for toll-like receptor 7 (TLR7) and BCRP (also known as the adenosine triphosphate-binding cassette transporter G2; gene symbol *ABCG2*) genotyping.

Cohort 1 (only): A PGx sample for CYP2C19 genotyping will be collected at screening as part of the inclusion/exclusion criteria.

Safety Assessments

Safety assessments will include a complete and symptom-driven physical examination, vital signs, height, weight, clinical laboratory tests, urine drug and alcohol assessments, 12-lead electrocardiogram (ECG), pregnancy testing, HBV and HCV testing, HIV-1 viral load test, CD4 cell count test, SARS-CoV-2 test, and assessment of AEs.

All safety assessments will be completed predose unless otherwise specified.

- *Complete physical examination:* Screening, follow-up, and early termination (ET) visits, if applicable
- *Symptom-driven physical examination:* every day during confinement, as needed, based on reported signs and symptoms

- *Vital signs (blood pressure, heart rate, oxygen saturation, and body temperature):*
  - Cohort 1: Screening, Period 1 Day 1 predose (within 1 hour before VES dosing) and 2, 4, 8, 12, and 24 hours postdose; Period 2 Day 2 predose (within 1 hour before VES dosing) and 2, 4, 8, 12, and 24 hours postdose; Period 3 Day 3 predose (within 1 hour before VES dosing) and 2, 4, 8, 12, and 24 hours postdose; at the follow-up visit, and at the ET visit, if applicable
  - Cohort 2: Screening, Period 1 Day 1 predose (within 1 hour before VES dosing) and 2, 4, 8, 12, and 24 hours postdose; Period 2 Day 6 predose (within 1 hour before VES dosing) and 2, 4, 8, 12, and 24 hours postdose; at the follow-up visit, and at the ET visit, if applicable
- *Height:* Screening
- *Weight:*
  - Cohort 1: Screening, Day −1 of each period, Period 1 Day 5, Period 2 Day 6, Period 3 Day 7, at the follow-up visit, and at the ET visit, if applicable
  - Cohort 2: Screening, Day −1 of each period, Period 1 Day 5, Period 2 Day 10, at the follow-up visit, and at the ET visit, if applicable
- *Coagulation panel:* Screening
- *Clinical laboratory tests (hematology, chemistry, calculated creatinine clearance, and urinalysis):*
  - Cohort 1: Screening, Day −1 of each period, Period 1 Day 5, Period 2 Day 6, Period 3 Day 7, at the follow-up visit, and at the ET visit, if applicable
  - Cohort 2: Screening, Day −1 of each period, Period 1 Day 5, Period 2 Day 10, at the follow-up visit, and at the ET visit, if applicable
- *Urine drug and alcohol assessments:*
  - Cohort 1: Screening, Day −1 of each period, Period 1 Day 3, Period 2 Day 4, and Period 3 Day 5
  - Cohort 2: Screening, Day −1 of each period, Period 1 Day 3, and Period 2 Day 8

  Note: On Day −1 (admission), 2 sets of safety laboratory results for hematology, chemistry, urinalysis, urine drug, and alcohol assessments will be collected upon study center admission. One will be sent to the central laboratory and the other will be sent to the site's local laboratory to obtain results in time for enrollment on Day 1.

  If a study center cannot perform a urine alcohol test or receive results from the local laboratory in time for enrollment on Day 1, then an alcohol breathalyzer test is acceptable.
- *12-lead ECG:*
  - Cohort 1: Screening; Period 1 Days 1, 2, and 5; Period 2 Days 2, 3, and 6; Period 3 Days 3, 4, and 7
  - Cohort 2: Screening, Period 1 Days 1, 2, and 5; and Period 2 Days 6, 7, and 10

- *Serum or urine pregnancy test (participants assigned female at birth of childbearing potential only):* Screening (serum), Day −1 of each period (serum or urine), at the follow-up visit (urine), and at the ET visit (urine), if applicable. For Cohort 2 only, an at-home urine pregnancy test will be completed 10 days after the last dose of RFB. Participants will be contacted by telephone to report at-home pregnancy test results.

  Note: Pregnancy test result is required prior to dosing. If Day −1 serum pregnancy test result is not available, a negative urine pregnancy test (performed locally) is required.
- *Follicle-stimulating hormone (participants assigned female at birth who are younger than 54 years, not on hormonal contraception, and who have stopped menstruating for at least 12 months but do not have documentation of ovarian hormonal failure):* Screening
- Hepatitis B virus, hepatitis C virus: Screening
- HIV-1 viral load testing:
  - Cohort 1: Screening, and Day −1 of Period 2 and Period 3
  - Cohort 2: Screening and Day −1 of Period 2
- CD4 cell count: Screening
- SARS-CoV-2: Day −1 of each period
- Assessment of AEs and concomitant medications will continue throughout the study. All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in protocol Appendix 11.4.

Protocol-Specific Discontinuation Criteria

Participant, cohort, and study-specific stopping criteria are detailed in Section 3.3.

Toxicity Management

After VES dosing, Grade 1 CRS, with influenza-like symptoms such as fever, fatigue, chills, myalgia, or headache without more severe manifestations such as changes in blood pressure or oxygen saturation, may be managed with supportive care (eg, paracetamol for myalgia or fever). If a participant experiences Grade 1 CRS, they will remain confined until symptoms resolve. For any Grade 2 or higher CRS, including hypotension and/or hypoxia, the participant will be immediately transferred to a hospital or emergency department for management in a monitored setting until symptoms resolve. Administration of steroids, intravenous fluid for hypotension, and supplemental oxygen for hypoxia should also be considered. **If a participant experiences treatment-related Grade 2 or higher CRS, dosing in that participant must be discontinued**.

Grading of Cytokine Release Syndrome

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Cytokine release syndrome	Fever with or without constitutional symptoms	Hypotension responding to fluids; hypoxia responding to < 40% O_2	Hypotension managed with one pressor; hypoxia requiring ≥ 40% O_2	Life-threatening consequences; urgent intervention indicated

National Cancer Institute Common Terminology Criteria for Adverse Events v5.0

Test Product, Dose, and Mode of Administration:

Cohort 1

In Period 2, COBI 150 mg will be administered on an empty stomach once daily on the mornings of Days 1 to 5; a single dose of VES 2 mg will be coadministered in the fasted state on the morning of Day 2.

In Period 3, VOR 400 mg will be administered on an empty stomach twice daily on Day 1, then VOR 200 mg will be administered on an empty stomach twice daily Days 2 to 6; a single dose of VES 2 mg will be coadministered in the fasted state on the morning of Day 3.

Cohort 2

In Period 2, RFB 300 mg will be administered on an empty stomach once daily on the mornings of Days 1 to 9; a single dose of VES 6 mg will be coadministered in the fasted state on the morning of Day 6.

Reference Therapy, Dose, and Mode of Administration:

Cohort 1

In Period 1, a single dose of VES 2 mg will be administered in a fasted state on the morning of Day 1.

Cohort 2

In Period 1, a single dose of VES 6 mg will be administered in a fasted state on the morning of Day 1.

Statistical Methods:

Pharmacokinetics:

Plasma concentrations and PK parameters will be listed and summarized for VES using descriptive statistics by treatment.

For Cohorts 1 and 2, an analysis of variance using a mixed-effects model with treatment as a fixed effect and participant as a random effect will be fitted to the natural logarithmic transformation of PK parameters for each analyte. Two-sided 90% CIs will be calculated for the ratios of geometric least-squares means (GLSMs) between test and reference treatments being compared.

Biomarkers:

The absolute level of PD biomarkers (including serum cytokines, ISGs mRNA, and immune cell phenotype), their change from baseline, and fold change from baseline will be listed and summarized using descriptive statistics by treatment within each cohort.

The absolute and normalized levels of TruCulture cytokines, as well as their association with serum PD biomarkers will be evaluated.

Safety:

The incidence of TEAEs and laboratory abnormalities will be summarized.

Select laboratory tests, vital signs, and ECG data will be summarized at scheduled visits and time points. All safety data will be provided in by-participant listings.

Sample Size:

With 18 evaluable participants per cohort, the estimated 2-sided 90% CI of the GLSM ratio of test versus reference treatments with regards to AUC_{inf} and C_{max} will be within (0.50, 2.00) with at least 90% probability if the true GLSM ratio was 1.0. This is assuming a root mean square error of no more than 0.6 on a natural logarithm scale, which is supported by the previous Study GS-US-234-0101. With 35% and 10% overage for Cohorts 1 and 2, a total sample size of 25 participants and 20 participants will be required for Cohorts 1 and 2; respectively.

STUDY SCHEMA

Figure 1. Study Schema

Cohort 1[a]

Screening[b] → Enroll N = 25 →

Period 1
Day 1
VES 2 mg

→ Washout[c] →

Period 2		
Day 1	Day 2	Days 3 to 5
COBI 150 mg	VES 2 mg + COBI 150 mg	COBI 150 mg

→ Washout[d] →

Period 3							
Day 1		Day 2		Day 3		Days 4 to 6	
AM	PM	AM	PM	AM	PM	AM	PM
VOR 400 mg	VOR 400 mg	VOR 200 mg	VOR 200 mg	VES 2 mg + VOR 200 mg	VOR 200 mg	VOR 200 mg	VOR 200 mg

Cohort 2

Screening[b] (DTG-based ART) → Enroll N = 20 →

Period 1
Day 1
VES 6 mg

→ Washout[c] →

Period 2		
Days 1 to 5	Day 6	Days 7 to 9
RFB 300 mg	VES 6 mg + RFB 300 mg	RFB 300 mg

ART = antiretroviral therapy; COBI = cobicistat; DTG = dolutegravir; RFB = rifabutin; SRT = safety review team; VES = vesatolimod; VOR = voriconazole

a An SRT review of the available safety data after the first 3 participants who are dosed with COBI in Cohort 1 up to and including Period 2 Day 3 should occur before initiation of the rest of the cohort.

b Prospective participants should be screened within 35 days prior to administration of the first dose of study drug.

c Washout period of 7 to 14 days between treatments in Period 1 Day 1 and Period 2 Day 1.

d Washout of period of 14 to 21 days between treatments in Period 2 Day 5 and Period 3 Day 1.

STUDY PROCEDURES TABLES

Table 1. Study Procedures Table for Cohort 1, Periods 1 and 2

Study Procedure	Screening[a]	Study Day														
		Period 1 (VES)							Period 2 (VES + COBI)							
		−1[b]	1	2[c]	3	4	5	Wash out[d]	−1[b]	1	2	3[c]	4	5	6	Wash out[e]
Written informed consent	X															
Eligibility criteria	X															
Complete medical history	X	X							X							
ART history[f]	X															
Complete physical examination	X															
Symptom-driven physical examination[g]		X	X	X					X	X	X	X				
Demographics	X															
Height	X															
Weight	X	X					X		X						X	
Vital signs[h]	X		X	X							X	X				
12-lead ECG[i]	X		X	X			X				X	X			X	
HIV-1 viral load	X								X							
CD4 cell count	X															
HBV and HCV testing[j]	X															
SARS-CoV-2[k]		X							X							
Urine drug and alcohol screen[u]	X	X			X				X				X			
Pregnancy test (women of childbearing potential)[l]	X	X							X							

Study Procedure	Screening[a]	Study Day														
		Period 1 (VES)							Period 2 (VES + COBI)							
		−1[b]	1	2[c]	3	4	5	Wash out[d]	−1[b]	1	2	3[c]	4	5	6	Wash out[e]
FSH (postmenopausal women)[m]	X															
Blood chemistry[u]	X	X					X		X						X	
Calculated CL_{cr}[u]	X	X					X		X						X	
Coagulation panel	X															
Hematology[u]	X	X					X		X						X	
Urinalysis[u]	X	X					X		X						X	
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X		X	X	X	X	X	X	X	
Enrollment			X													
Confinement[n]		X	X	X					X	X	X	X				
VES dosing			X								X					
COBI dosing										X	X	X	X	X		
Plasma VES and perpetrator PK[o]			X	X	X	X	X				X	X	X	X	X	
Serum biomarkers[p]			X	X	X		X				X	X	X		X	
Whole blood ISG mRNA[q]			X	X	X	X	X				X	X	X	X	X	
PGx (TLR7 and BCRP)[r]			X													
PGx CYP2C19[s]	X															
Immune cell phenotyping[t]			X	X		X	X				X	X		X	X	

AE = adverse event; ART = antiretroviral therapy; BCRP = breast cancer resistance protein; CD4 = clusters of differentiation 4; CL_{cr} = creatinine clearance; COBI = cobicistat; CYP = cytochrome P450 enzyme; CRS = cytokine release syndrome; ECG = electrocardiogram; FSH = follicle-stimulating hormone; HBsAg = hepatitis B virus surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; ISG = interferon-stimulated genes; mRNA = messenger RNA; PGx = pharmacogenetics; PK = pharmacokinetics; TLR7 = toll-like receptor 7; VES = vesatolimod

a Prospective participants should be screened within 35 days prior to administration of the first dose of study drug.
b Admission to clinic.
c Discharge from clinic.

d There will be a washout period of 7 to 14 days between treatments in Period 1 Day 1 and Period 2 Day 1. Participants should inform the site of any AE during the washout period.
e There will be a washout period of 14 to 21 days between treatments in Period 2 Day 5 and Period 3 Day 1 . Participants should inform the site of any AE during the washout period.
f Collect ART history for at least the past 12 months.
g Every day during confinement, as needed, based on reported signs and symptoms.
h Vital signs include blood pressure, heart rate, oxygen saturation, and body temperature. Vital signs will be collected at predose (within 1 hour before VES dosing) and 2, 4, 8, 12, and 24 hours after each dose of VES.
i 12-lead ECGs will be collected after the participant has rested for at least 5 minutes in the supine position. A 12-lead ECG will be collected 2 hours after each dose of VES.
j HBV core antibody, HBsAg, and HCV antibody at screening.
k COVID-19 testing in accordance with the local guidelines will be conducted and reviewed per site-specific policy at admission (Day −1) and as needed prior to the next scheduled test based upon symptoms. Termination of the cohort for any positive viral test result will be at the discretion of the sponsor and the investigator.
l For participants assigned female at birth and of childbearing potential. Serum pregnancy test is required at screening. Serum or urine pregnancy test at Day −1 of each period is acceptable. Pregnancy test result is required prior to dosing. If Day −1 serum pregnancy test result is not available, a negative urine pregnancy test (performed locally) is required.
m For participants assigned female at birth who are younger than 54 years, not on hormonal contraception, and who have stopped menstruating for at least 12 months but do not have documentation of ovarian hormonal failure.
n In Period 1, participants will be confined beginning Day −1 until completion of assessments on Day 2. In Period 2, participants will be confined beginning on Day -1 until completion of assessments on Day 3. Participants may remain confined for a longer duration within each treatment period if this is preferred. If a participant is experiencing signs and symptoms of CRS, the participant will remain confined (for CRS symptoms of Grade 1) or immediately be transferred to a hospital or emergency department (for CRS symptoms of ≥ Grade 2) until symptoms resolve.
o VES and perpetrator PK samples will be collected at predose (within 0.5 hours before dosing) and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 48, 72, and 96 hours after each dose of VES. Time windows allowed for PK samples to be collected are provided in Table 8.
p Serum biomarker samples will be collected at predose (within 0.5 hours before dosing) and 4, 8, 12, 24, 48, and 96 hours after each dose of VES. A time window of ± 10% will be allowed for biomarker samples collected through 8 hours postdose. Biomarker samples collected beyond 8 hours postdose will have a ± 30 minute window.
q Whole blood samples for ISG mRNA expression and transcriptional profile will be collected predose (within 0.5 hours before dosing) and 8, 12, 24, 48, 72, and 96 hours postdose relative to VES. A time window of ± 10% will be allowed for whole blood samples collected at 8 hours postdose. Whole blood samples collected beyond 8 hours postdose will have a ± 30-minute window.
r A PGx sample will be collected on Day 1 (preferably) or at any other time during the study.
s Results must be reviewed prior to enrollment.
t Whole blood sample for immune cell phenotyping will be collected predose (within 0.5 hours before dosing), and 24, 72, and 96 hours postdose relative to VES. Whole blood samples collected postdose will have a ± 30-minute window.
u On Day −1 (admission), 2 sets of safety laboratory results for hematology, chemistry, urinalysis, urine drug, and alcohol assessments will be collected upon study center admission. One will be sent to the central laboratory and the other will be sent to the site's local laboratory to obtain results in time for enrollment on Day 1. If a study center cannot perform a urine alcohol test or receive results from the local laboratory in time for enrollment on Day 1, then an alcohol breathalyzer test is acceptable.

All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in protocol Appendix 11.4.

Table 2. Study Procedures Table for Cohort 1, Period 3

	Study Day								
	Period 3 (VES + VOR)								
Study Procedure	**−1[a]**	**1**	**2**	**3**	**4[b]**	**5**	**6**	**7**	**Follow-up[c]/ET[d]**
Complete physical examination									X
Symptom-driven physical examination[e]	X	X	X	X	X				
Weight	X							X	X
Vital signs[f]				X	X				X
12-lead ECG[g]				X	X			X	
HIV-1 viral load	X								
SARS-CoV-2[h]	X								
Urine drug and alcohol screen[q]	X					X			
Pregnancy test (women of childbearing potential)[i]	X								X
Blood chemistry[q]	X							X	X
Calculated CL_{cr}[q]	X							X	X
Hematology[q]	X							X	X
Urinalysis[q]	X							X	X
Adverse events	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X
Confinement[j]	X	X	X	X	X				
VES dosing[k]				X					
VOR dosing[l]		X	X	X	X	X	X		
Plasma VES and perpetrator PK[m]				X	X	X	X	X	
Serum biomarkers[n]				X	X	X		X	
Whole blood ISG mRNA[o]				X	X	X	X	X	
Immune cell phenotyping[p]				X	X		X	X	

CL_{cr} = creatinine clearance; CRS = cytokine release syndrome; ECG = electrocardiogram; ET = early termination; ISG = interferon-stimulated genes; mRNA = messenger RNA; PK = pharmacokinetics; VES = vesatolimod; VOR = voriconazole

a Admission to clinic.
b Discharge from clinic.
c Participants will return for an in-clinic follow-up visit 10 (± 3) days after the last dose of VES.
d Assessments will be performed within 72 hours of ET from the study, if possible.
e Every day during confinement, as needed, based on reported signs and symptoms.
f Vital signs include blood pressure, heart rate, oxygen saturation, and body temperature. Vital signs will be collected at predose (within 1 hour before VES dosing) and 2, 4, 8, 12, and 24 hours after the VES dose in Period 3.
g 12-lead ECGs will be collected after the participant has rested for at least 5 minutes in the supine position. A 12-lead ECG will be collected 2 hours after the VES dose in Period 3.
h COVID-19 testing in accordance with the local guidelines will be conducted and reviewed per site-specific policy at admission (Day −1) and as needed based upon symptoms. Termination of the cohort for any positive viral test result will be at the discretion of the sponsor and the investigator.
i For participants assigned female at birth and of childbearing potential. Serum pregnancy test is required at screening. Serum or urine pregnancy test at Day −1 of each period is acceptable. Pregnancy test result is required prior to dosing. If Day −1 serum pregnancy test result is not available, a negative urine pregnancy test (performed locally) is required. Urine pregnancy testing is repeated at the follow-up visit and ET visit, if applicable.
j In Period 3, participants will be confined beginning on Day −1 until completion of assessments on Day 4. Participants may remain confined for a longer duration if this is preferred. If a participant is experiencing signs and symptoms of CRS, the participant will remain confined (for CRS symptoms of Grade 1) or immediately be transferred to a hospital or emergency department (for CRS symptoms of ≥ Grade 2) until symptoms resolve.
k VES will be dosed in the morning.
l VOR will be dosed twice daily.
m VES and perpetrator PK samples will be collected at predose (within 0.5 hours before dosing) and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 48, 72, and 96 hours after administration of VES. Time windows allowed for PK samples to be collected are provided in Table 8.
n Serum biomarker samples will be collected at predose (within 0.5 hours before dosing) and 4, 8, 12, 24, 48, and 96 hours after administration of VES. A time window of ± 10% will be allowed for biomarker samples collected through 8 hours postdose. Biomarker samples collected beyond 8 hours postdose will have a ± 30-minute window.
o Whole blood samples for ISG mRNA expression and transcriptional profile will be collected predose (within 0.5 hours before dosing) and 8, 12, 24, 48, 72, and 96 hours postdose relative to VES. A time window of ± 10% will be allowed for whole blood samples collected at 8 hours postdose. Whole blood samples collected beyond 8 hours postdose will have a ± 30 minute window.
p Whole blood sample for immune cell phenotyping will be collected predose (within 0.5 hours before dosing), and 24, 72, and 96 hours postdose relative to VES. Whole blood samples collected postdose will have a ± 30-minute window.
q On Day −1 (admission), 2 sets of safety laboratory results for hematology, chemistry, urinalysis, urine drug, and alcohol assessments will be collected upon study center admission. One will be sent to the central laboratory and the other will be sent to the site's local laboratory to obtain results in time for enrollment on Day 1. If a study center cannot perform a urine alcohol test or receive results from the local laboratory in time for enrollment on Day 1, then an alcohol breathalyzer test is acceptable.

All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in protocol Appendix 11.4.

Table 3. Study Procedures Table for Cohort 2, Periods 1 and 2

Study Procedure	Screening[a]	Study Day																	Follow-up[e]/ET[f]	Telephone contact[g]
		Period 1 (VES)						Wash out[d]	Period 2 (VES + RFB)											
		−1[b]	1	2[c]	3	4	5		−1[b]	1	2	3	4	5	6	7[c]	8	9	10	
Written informed consent	X																			
Eligibility criteria	X																			
Complete medical history	X	X							X											
ART history[h]	X																			
Complete physical examination	X																		X	
Symptom-driven physical examination[i]		X	X	X					X	X	X	X	X	X	X	X				
Demographics	X																			
Height	X																			
Weight	X	X					X		X										X	X	
Vital signs[j]	X		X	X											X	X				X	
12-lead ECG[k]	X		X	X			X								X	X			X		
HIV-1 viral load	X								X												
CD4 cell count	X																				
HBV and HCV testing[l]	X																				
SARS-CoV-2[m]		X							X												
Urine drug and alcohol screen[n]	X	X			X				X								X				
Pregnancy test (women of childbearing potential)[o]	X	X							X											X	X

Study Procedure	Screening[a]	Study Day																	Follow-up[e]/ET[f]	Telephone contact[g]
		Period 1 (VES)						Wash out[d]	Period 2 (VES + RFB)											
		−1[b]	1	2[c]	3	4	5		−1[b]	1	2	3	4	5	6	7[c]	8	9	10	
FSH (postmenopausal women)[p]	X																			
Blood chemistry[n]	X	X					X		X										X	X
Calculated CL_{cr}[n]	X	X					X		X										X	X
Coagulation panel	X																			
Hematology[n]	X	X					X		X										X	X
Urinalysis[n]	X	X					X		X										X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Enrollment			X																	
Confinement[o]		X	X	X					X	X	X	X	X	X	X	X				
VES dosing			X												X					
RFB dosing										X	X	X	X	X	X	X	X	X		
Plasma VES and perpetrator PK[r]			X	X	X	X	X								X	X	X	X	X	
Serum biomarkers[s]			X	X	X		X								X	X	X		X	
Whole blood ISG mRNA[t]			X	X	X	X	X								X	X	X	X	X	
PGx (TLR7 and BCRP)[u]			X																	
Immune cell phenotyping[v]			X	X		X	X								X	X		X	X	
TruCulture cytokine response[w]			X																	

ART = antiretroviral therapy; BCRP = breast cancer resistance protein; CD4 = clusters of differentiation 4; CL_{cr} = creatinine clearance; CRS = cytokine release syndrome; ECG = electrocardiogram; ET = early termination; FSH = follicle-stimulating hormone; HBsAg = hepatitis B virus surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; ISG = interferon-stimulated genes; mRNA = messenger RNA; PGx = pharmacogenetics; PK = pharmacokinetics; RFB = rifabutin; TLR7 = toll-like receptor 7; VES = vesatolimod

a Prospective participants should be screened within 35 days prior to administration of the first dose of study drug.
b Admission to clinic.
c Discharge from clinic.
d There will be a washout period of 7 to 14 days between treatments in Period 1 Day 1 and Period 2 Day 1. Participants should inform the site of any AE during the washout period.
e Participants will return for an in-clinic follow-up visit 10 (± 3) days after the last dose of VES.
f Assessments will be performed within 72 hours of ET from the study, if possible.
g For participants assigned female at birth of childbearing potential, an at-home urine pregnancy test will be completed 10 days after the last dose of RFB. Participants will be contacted by telephone to report at-home pregnancy test results.
h Collect ART history for at least the past 12 months.
i Every day during confinement, as needed, based on reported signs and symptoms.
j Vital signs include blood pressure, heart rate, oxygen saturation, and body temperature. Vital signs will be collected at predose (within 1 hour before VES dosing) and 2, 4, 8, 12, and 24 hours after each dose of VES.
k 12-lead ECGs will be collected after the participant has rested for at least 5 minutes in the supine position. A 12-lead ECG will be collected 2 hours after each dose of VES.
l HBV core antibody, HBsAg, and HCV antibody at screening.
m COVID-19 testing in accordance with the local guidelines will be conducted and reviewed per site-specific policy at admission (Day −1) and as needed prior to the next scheduled test based upon symptoms. Termination of the cohort for any positive viral test result will be at the discretion of the sponsor and the investigator.
n On Day −1 (admission), 2 sets of safety laboratory results for hematology, chemistry, urinalysis, urine drug, and alcohol assessments will be collected upon study center admission. One will be sent to the central laboratory and the other will be sent to the site's local laboratory to obtain results in time for enrollment on Day 1. If a study center cannot perform a urine alcohol test or receive results from the local laboratory in time for enrollment on Day 1, then an alcohol breathalyzer test is acceptable.
o For participants assigned female at birth and of childbearing potential. Serum pregnancy test is required at screening. Serum or urine pregnancy test at Day −1 of each period is acceptable. Pregnancy test result is required prior to dosing. If Day −1 serum pregnancy test result is not available, a negative urine pregnancy test (performed locally) is required. Urine pregnancy testing is repeated at the follow-up visit and ET visit, if applicable.
p For participants assigned female at birth who are younger than 54 years, not on hormonal contraception, and who have stopped menstruating for at least 12 months but do not have documentation of ovarian hormonal failure.
q In Period 1, participants will be confined beginning Day −1 until completion of assessments on Day 2. In Period 2, participants will be confined beginning on Day -1 until completion of assessments on Day 7. Participants may remain confined for a longer duration within each treatment period if this is preferred. If a participant is experiencing signs and symptoms of CRS, the participant will remain confined (for CRS symptoms of Grade 1) or immediately be transferred to a hospital or emergency department (for CRS symptoms of ≥ Grade 2) until symptoms resolve.
r VES and perpetrator PK samples will be collected at predose (within 0.5 hours before dosing) and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 48, 72, and 96 hours after each dose of VES. Time windows allowed for PK samples to be collected are provided in Table 8.
s Serum biomarker samples will be collected at predose (within 0.5 hours before dosing) and 4, 8, 12, 24, 48, and 96 hours after each dose of VES. A time window of ± 10% will be allowed for biomarker samples collected through 8 hours postdose. Biomarker samples collected beyond 8 hours postdose will have a ± 30-minute window.
t Whole blood samples for ISG mRNA expression and transcriptional profile will be collected predose (within 0.5 hours before dosing) and 8, 12, 24, 48, 72, and 96 hours postdose relative to VES. A time window of ± 10% will be allowed for whole blood samples collected at 8 hours postdose. Whole blood samples collected beyond 8 hours postdose will have a ± 30-minute window.
u A PGx sample will be collected on Day 1 (preferably) or at any other time during the study.
v Whole blood sample for immune cell phenotyping will be collected predose (within 0.5 hours before dosing), and 24, 72, and 96 hours postdose relative to VES. Whole blood samples collected postdose will have a ± 30 minute window.

w Whole blood sample for TruCulture cytokine response will be collected on Period 1 Day 1 (predose).

All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in protocol Appendix 11.4.

1. INTRODUCTION

1.1. Background

Human immunodeficiency virus type-1 (HIV-1) infection is a life-threatening and serious disease that is of major public health interest around the world. A 2021 report by the Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that 79.3 million people have been infected with HIV since the start of the epidemic, contributing to 36.3 million deaths from AIDS-related illnesses {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2021}. Untreated infection leads to deterioration in immune function and death. Although antiretroviral therapy (ART) has been associated with a dramatic decrease in AIDS-related morbidity and mortality {Mocroft 1998, Palella 1998, Sterne 2005}, there is still an urgent medical need to develop new therapies and approaches to eradicate HIV. Current therapy is associated with challenges with tolerability, long-term adherence and safety, drug-drug interactions, and expense. Persistent HIV infection may also be associated with psychosocial stigma. Despite the availability of chronic treatment, morbidity and mortality due to HIV infection remain high due to the persistence of a latent HIV reservoir, which may contribute to ongoing inflammation-driven disease. Persistent viral reservoirs fuel rebound viremia when treatment ceases. Thus, the discovery and development of therapeutic interventions that can eradicate or control HIV reservoirs, leading to long-term ART-free remission or HIV cure, is a major priority.

The innate immune response modulates the production of type I interferons (IFNs; eg, interferon-alpha [IFN-α]) and promotes the cross-priming of cytotoxic T lymphocytes, resulting in an efficient immune response {Iwasaki 2010, Knolle 2012}. A key innate immune effector cell is the plasmacytoid dendritic cell (pDC) that expresses toll-like receptor 7 (TLR7). Following TLR7 stimulation, pDCs produce type I IFNs, resulting in increased transcription of interferon-stimulated genes (ISG), many of which have antiviral activity {Sadler 2008}. TLR7 stimulation also activates pDCs, monocytes, natural killer cells, and CD4 and CD8 T cells {Riddler 2020, SenGupta 2021, Tel 2013}. Finally, TLR7 is expressed by B lymphocytes, and TLR7 activation results in polyclonal expansion and differentiation towards immunoglobulin-producing plasma cells, providing a humoral component to the adaptive immune response {Bekeredjian-Ding 2005}.

During HIV-1 infection, levels of IFN-α and ISG messenger RNA (mRNA) increase, which is consistent with TLR7 stimulation; B cell and CD8 T-cell responses to virus are also detected in most individuals with HIV-1. However, in most cases, these immune responses are not sufficient to control the infection without ART. Activation of TLR7 can generate a variety of effects and enhance innate and adaptive immunity that may provide a novel treatment paradigm for people with HIV-1 infection.

Vesatolimod (VES) is a TLR7 agonist currently in clinical development for the treatment and remission of HIV-1 infection. Vesatolimod has been shown to induce ISG mRNA expression and production of cytokines and chemokines, and to induce activation of CD4 and CD8 T lymphocytes in HIV-1-infected individuals (virologically suppressed on ART). The ability of

VES to increase the cytotoxic activity of HIV-specific T lymphocytes and activate phagocytic cells, improving antibody-dependent cell-mediated cytotoxicity in vitro, suggests that its immunomodulatory effect could enhance the antiviral activity of HIV-1 broadly neutralizing antibodies (bNAbs). In fact, in rhesus macaque studies, sequential regimens including TLR7 agonists and either therapeutic vaccination or bNAbs have led to simian-human immunodeficiency virus ART-free viral control {Borducchi 2016, Borducchi 2018}. Similar results have now been demonstrated in a chronically-infected nonhuman primate model {Mercado 2020}.

Vesatolimod is a substrate of cytochrome P450 enzyme (CYP)3A, P-glycoprotein (P-gp), and breast cancer resistance protein (BCRP). This study will evaluate the impact of cobicistat (COBI) (P-gp, BCRP, and strong CYP3A inhibitor), voriconazole (VOR) (strong CYP3A inhibitor), and rifabutin (RFB) (moderate CYP3A inducer) on the pharmacokinetics (PK) and pharmacodynamics (PD) of VES as well as the safety in virologically suppressed adults with HIV-1 on ART to inform future studies of VES.

1.2. Background on Study Interventions

1.2.1. Vesatolimod

1.2.1.1. General Information

Vesatolimod is an orally administered TLR7 agonist in development for the treatment and remission of HIV infection. Data in vitro have shown that VES is a potent and selective TLR7 receptor agonist with greater than 30-fold selectivity for TLR7 (32-fold based on half-maximal effective concentration and 81-fold based on minimum effective concentration) over TLR8, with no detectable stimulation of other human toll-like receptors at concentrations up to 100 μM.

For further information on VES, refer to the investigator's brochure (IB), including information on the following:

- Nonclinical PK and in vitro metabolism
- Nonclinical pharmacology and toxicology
- Clinical experience

1.2.1.2. Nonclinical Pharmacokinetics and Drug Interaction Potential

High systemic clearance of VES was observed in the mouse, rat, dog, and monkey. Plasma protein binding in human plasma is 81.5%. Metabolism is the main route of elimination for VES, and CYP3A is the enzyme predominantly responsible for VES metabolism. When tested in human hepatic microsomes, ketoconazole (a CYP3A-selective inhibitor) had the largest effect on the metabolism of VES (90% inhibition). Based on in vitro assays, VES is also a substrate of P-gp and BCRP. Therefore, VES concentrations may be altered in the presence of concomitant medications that inhibit or induce these drug metabolizing enzymes and transporters.

Vesatolimod is not a perpetrator of drug interactions; based on in vitro studies, VES is not predicted to be a clinically relevant inhibitor of the transporters P-gp, BCRP, organic anion transporting polypeptide (OATP)1B1, OATP1B3, organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)1, OCT2, multidrug and toxin extrusion 1, bile salt export pump, multidrug resistance-associated protein, or the drug metabolizing enzymes CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, and was not an inducer of the acetylcholine receptor or the constitutive androstane receptor.

1.2.1.3. Clinical Studies of Vesatolimod in People With HIV-1

Safety data from 2 Phase 1b Studies GS-US-382-1450 and GS-US-382-3961 suggest that VES is generally well tolerated in people with HIV-1 (PWH) on ART who received multiple doses up to 12 mg each. The most common drug-related treatment-emergent adverse events (TEAEs) were flu-like symptoms such as pyrexia, chills, headache, myalgia, and fatigue. The majority of adverse events (AEs) were Grade 1 or 2. Few serious adverse events (SAEs) or Grade 3 to 4 AEs were observed. Grade 3 events included gastritis viral, gout, arthralgia, and sciatica (all observed in 1 participant) and lower abdominal pain. Serious adverse events included chronic gastritis (1 participant) and diverticulitis (1 participant, concurrent with the lower abdominal pain Grade 3 AE mentioned above).

Pharmacokinetic assessments for VES showed that AUC_{last}, AUC_{inf}, and C_{max} increased across the dose range of 1 to 12 mg in PWH (Table 4). Across doses, median T_{max} was 1.0 to 3.0 hours and $t_{1/2}$ was 9 to 19 hours. As no accumulation of VES is anticipated based on the observed half-life, the PK parameters observed after the first dose are representative of chronic exposure following every other week dosing.

Table 4. Summary of Vesatolimod Pharmacokinetic Parameters (Study GS-US-382-1450)

PK Parameter	VES Dose						
	1 mg	2 mg	4 mg	6 mg	8 mg	10 mg	12 mg
AUC_{inf} (h*pg/mL)	4573.9 (78.5)	9938.7 (40.2)	27,402.1 (69.6)	44,078.1 (76.0)	50,971.5 (88.6)	62,872.1 (78.0)	101,112.8 (49.3)
AUC_{last} (h*pg/mL)	2757.8 (70.1)	7736.5 (55.5)	21,774.9 (80.0)	38,196.1 (73.7)	44,930.4 (82.0)	57,341.9 (77.1)	94,339.6 (49.8)
C_{max} (pg/mL)	461.0 (72.5)	972.8 (38.9)	1990.3 (62.1)	3088.3 (66.3)	6680.0 (120.4)	5833.3 (71.7)	11,988.3 (71.5)
T_{max} (h)	1.50 (1.00, 4.00)	1.75 (0.50, 4.00)	1.00 (1.00, 2.00)	2.00 (1.00, 4.00)	1.00 (1.00, 2.00)	2.01 (2.00, 3.97)	3.00 (2.00, 4.00)
$t_{1/2}$ (h)	9.29 (7.98, 12.15)	14.65 (8.37, 20.15)	19.21 (14.14, 24.04)	17.37 (16.25, 18.41)	12.03 (10.86, 15.30)	14.44 (13.36, 15.19)	13.47 (12.38, 15.78)

Data are presented as mean (%CV), except for T_{max} and $t_{1/2}$, which are presented as median (Q1, Q3).

1.2.2. Cobicistat

Cobicistat is a CYP3A inhibitor indicated to increase systemic exposure of atazanavir or darunavir (once daily dosing regimen) in combination with other antiretroviral agents in the treatment of HIV-1 infection in adults. Cobicistat is also coformulated with ARTs, such as elvitegravir + nucleoside reverse transcriptase inhibitors (NRTIs). The recommended dosage of COBI in adults is 150 mg orally once daily.

In adults the most common adverse reactions (Grades 2 to 4) and reported in more than 2% of participants in the COBI group (N = 344) were jaundice (6%), rash (5%), ocular icterus (4%), nausea, diarrhea, and headache (2% each). The proportion of participants who discontinued study drug due to AEs, regardless of severity, was 11% in the COBI group.

Cobicistat causes increases in serum creatinine and decreases in estimated creatinine clearance due to inhibition of tubular secretion without affecting actual renal glomerular function. The most common Grade 3 or 4 laboratory abnormality (incidence ≥ 10%) in the COBI group was increased total bilirubin (> 2.5 × upper limit of normal [ULN]; 73%).

For further information on COBI, refer to the United States (US) prescribing information for Tybost (COBI) {TYBOST 2021}.

1.2.3. Voriconazole

Voriconazole is a synthetic broad-spectrum antifungal agent for use in the treatment of systemic fungal infections such as invasive aspergillosis, candidemia, disseminated candidiasis in skin, oral thrush, and serious infections caused by *Scedosporium apiospermum* and *Fusarium* species. The recommended oral maintenance dose in adults is 200 mg every 12 hours. In adults (N = 1655), the most common adverse reactions (incidence ≥ 2%) in clinical studies were visual disturbances (18.7%), fever (5.7%), nausea (5.4%), rash (5.3%), vomiting (4.4%), chills (3.7%), headache (3.0%), liver function test increased (2.7%), tachycardia (2.4%), and hallucinations (2.4%). The adverse reactions which most often led to discontinuation of VOR were elevated liver function tests, rash, and visual disturbances.

Voriconazole is a strong inhibitor of CYP3A and also inhibits CYP2C19 and CYP2C9; it's major metabolite also inhibits the metabolic activity of CYP450 enzymes and therefore, there is potential for VOR and its major metabolite to increase the systemic exposure of other drugs metabolized by these CYP450 enzymes.

For further information on VOR, refer to the US prescribing information for VFEND (VOR) {VFEND® 2021}.

1.2.4. Rifabutin

Rifabutin is a rifamycin antimycobacterial agent indicated for the prevention of disseminated *Mycobacterium avium* complex disease in people with advanced HIV infection. The recommended dose in adults is 300 mg once daily. In adults (N = 566), the most common AEs (incidence ≥ 2%) in clinical studies were discolored urine (30%), rash (11%), leucopenia (10%), nausea (6%), abdominal pain (4%), diarrhea, dyspepsia, eructation, headache, nausea and vomiting, and taste perversion (3% each), and anorexia, fever, flatulence, and myalgia (2% each). Primary reasons for discontinuation of rifabutin in clinical studies were rash (4%), gastrointestinal intolerance (3%), and neutropenia (2%).

Rifabutin induces CYP3A enzymes and therefore may reduce the plasma concentrations of drugs metabolized by those enzymes.

For further information on RFB, refer to the US prescribing information for Mycobutin (RFB) {MYCOBUTIN® 2021}.

1.3. Rationale for This Study

Vesatolimod is a substrate of P-gp, BCRP, and CYP3A. Vesatolimod exposure is expected to increase when coadministered with P-gp, BCRP, and/or CYP3A inhibitors and to decrease when coadministered with inducers. Therefore, this study will evaluate the impact of 3 perpetrator drugs on the PK of VES.

Cohort 1 - Period 2: Cobicistat (COBI)

- Cobicistat is a common component of ART and is a P-gp, BCRP, and strong CYP3A inhibitor and expected to be a worst-case perpetrator for inhibition

Cohort 1 - Period 3: Voriconazole (VOR)

- Voriconazole is a strong CYP3A inhibitor that does not inhibit P-gp or BCRP

Cohort 2 – Period 2: Rifabutin (RFB)

- Rifabutin is a moderate CYP3A inducer

Comparing results of Cohort 1 and Cohort 2 may provide information regarding the relative importance of transporters and drug metabolizing enzymes for VES disposition. All cohorts will be evaluated in an open-label design, which is appropriate because the primary endpoint is an objective measure of VES PK.

The open-label, single sequence study design of Cohorts 1 and 2 allows for the within-participant comparison of VES PK when administered alone and in combination with the perpetrator of drug interaction. The within-participant design minimizes the impact of factors other than the interacting drug on VES PK.

Cohort 1: The ART regimens permitted in Cohort 1 (bictegravir [BIC], dolutegravir [DTG], raltegravir [RAL], or doravirine [DOR] + NRTIs) were selected because these ARTs are not expected to impact VES PK and because the impact of COBI and VOR on the ART concentrations are not expected to be clinically meaningful based on drug interaction data in the prescribing information for these medications. Because VOR has been associated with QT prolongation, other drugs with the potential for QT prolongation (such as rilpivirine) are not permitted in Cohort 1.

Cohort 2: The ART regimens permitted in Cohort 2 (DTG/abacavir [ABC]/lamivudine [3TC], DTG/3TC, or DTG + NRTIs) were selected because these ARTs are not expected to impact VES PK and because the impact of RFB on these ART concentrations are not expected to be clinically meaningful based on drug interaction data in the prescribing information for these medications.

1.4. Rationale for the Dose Selection of Study Drugs

Cohort 1: Increases in VES exposure are expected when VES is coadministered with strong CYP3A inhibitors in Period 2 (COBI) and Period 3 (VOR). Based on physiologically based pharmacokinetic (PBPK) modeling, a VES dose of 2 mg, in combination with COBI or VOR, is predicted to achieve VES AUC in the range of those achieved with a therapeutic dose of VES (6 to 8 mg) in the absence of an inhibitor. The C_{max} value for the 2 mg dose of VES in combination with COBI or VOR is predicted to be below C_{max} for single 6 mg and 8 mg doses of VES in the absence of an inhibitor. Therefore, a dose of VES 2 mg has been selected for Cohort 1. As COBI (which also inhibits P-gp) will be dosed before VOR in Cohort 1 and inhibits CYP3A in a similar mechanism and magnitude to VOR, the sentinel group of participants evaluating the COBI + VES combination will mitigate the risk of overexposure to VES when dosed with VOR.

Cobicistat will be administered at the approved dose of 150 mg once daily, for the treatment of HIV-1 infection in adults starting on the day prior to VES administration and continuing through the duration of PK sampling. Based on literature and PBPK modeling, this COBI regimen is expected to provide near maximal inhibition of CYP3A {Mathias 2010}.

Voriconazole will be administered as a loading dose of 400 mg twice daily, then as 200 mg twice daily which are the approved loading and maintenance doses for adults weighing 40 kg or more. Voriconazole dosing will start 2 days prior to VES administration and continue through the duration of PK sampling. Based on literature and PBPK modeling, this VOR regimen is expected to provide near maximal inhibition of CYP3A {Katzenmaier 2011}.

Cohort 2: A therapeutic dose of VES 6 mg has been selected to allow accurate assessment of PK changes with an inducer, which is expected to decrease VES concentrations.

Rifabutin will be administered at the approved dose in adults of 300 mg once daily starting 5 days prior to VES administration and continuing through to 3 days after.

1.5. Risk/Benefit Assessment for the Study

Potential risks of a participant's study involvement include unknown AEs, general risks associated with frequent clinic visits and laboratory blood draws. Based on the current available clinical data, potential risks associated with VES include transient influenza-like symptoms, such as chills, pyrexia, aches, and headache and cytokine release syndrome (CRS). In completed and ongoing studies of VES, the majority of the influenza-like symptoms have been mild (302 of 387 flu-like AEs, 78.0%) and transient. One healthy volunteer who received 1 dose of VES 8 mg coadministered with elipovimab (an HIV-1 bNAb) 250 mg experienced a Grade 3 SAE) of CRS that was considered related to VES, leading to treatment and observation in the hospital followed by full recovery. The other 3 healthy volunteers receiving this regimen did not experience SAEs. At the 12 mg dose level of VES in healthy volunteers (Study GS-US-243-0101), nongraded nonclinically significant decreases in platelet counts were observed in some participants, which resolved within 2 days without intervention. Treatment-emergent platelet decreases have not been observed at doses up to 12 mg in PWH in Study GS-US-382-1450 or in Study GS-US-382-3961. Safety laboratory values, including complete blood count and chemistry panels, will be regularly monitored throughout the study.

Strategies to mitigate these risks include close monitoring of participants' clinical status, laboratory values, and AEs. Parameters for discontinuation of the study drug due to AEs will be well defined and closely followed.

There is no direct benefit to participants in this study; however, data from this study will support the development of VES.

An infectious disease pandemic may pose additional risks to study drug availability, study visit schedule, and adherence to protocol-specified safety monitoring or laboratory assessments. Refer to Appendix 11.2 for further details on the risks and risk mitigation strategy.

1.6. Compliance

This study will be conducted in compliance with this protocol and in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

2. OBJECTIVES AND ENDPOINTS

Primary Objective(s)	Primary Endpoint(s)
To evaluate the impact of the following drugs on VES PK • Cobicistat (P-gp, BCRP, and strong CYP3A inhibitor) • Voriconazole (strong CYP3A inhibitor) • Rifabutin (moderate CYP3A inducer) To evaluate the safety of VES administered alone and in combination with inhibitors and inducers of metabolizing enzymes and transporters involved in VES disposition	Primary PK parameters throughout the study • VES AUC_{last}, AUC_{inf}, C_{max} Secondary PK parameters throughout the study • VES $\%AUC_{exp}$, T_{max}, C_{last}, T_{last}, λ_z, $t_{1/2}$, CL/F, V_z/F Safety parameters • Incidence of TEAEs and laboratory abnormalities throughout the study
CCI [redacted]	[redacted]
[redacted]	[redacted]

3. STUDY DESIGN

3.1. Study Design

This protocol describes an open-label, multicohort Phase 1 study to evaluate the impact of inhibitors and inducers of CYP3A and/or P-gp on the PK and PD of VES in virologically suppressed adults with HIV-1 on ART. Approximately 45 participants will be enrolled. An overview of the study design is described below and shown in Figure 1.

The study will be conducted in 2 cohorts:

- Cohort 1: An open-label, single sequence cohort to evaluate the impact of COBI (P-gp, BCRP, and strong CYP3A inhibitor) and VOR (strong CYP3A inhibitor) on VES PK and PD
- Cohort 2: An open-label, single sequence cohort to evaluate the impact of RFB (moderate CYP3A inducer) on VES PK and PD

3.1.1. Safety Review Team and Charter

A safety review team (SRT) will be established to assess relevant and available safety data for the first 3 participants in Cohort 1 who are dosed with COBI (up to and including Period 2 Day 3) to decide to continue or halt enrollment of additional participants in Cohort 1.

An SRT charter defining the team membership, meeting conduct, and decision-making process will be agreed upon by all team members before the first meeting. The data reviewed at the team meetings will be defined in the charter. The quality control checks performed on the data reviewed will also be described in the charter.

Source data verification may not be performed before SRT meetings. Alternative data quality control checks that are performed on data are described in the SRT charter (or similar document).

3.2. Duration of Dosing

Duration of dosing for each cohort is as follows:

- Cohort 1: VES will be administered as a single dose in Periods 1, 2, and 3; COBI will be administered for 5 days in Period 2; and VOR will be administered for 6 days in Period 3. There will be a washout period of 7 to 14 days between treatments in Period 1 Day 1 and Period 2 Day 1 and a washout period of 14 to 21 days between treatments in Period 2 Day 5 and Period 3 Day 1.
- Cohort 2: VES will be administered as a single dose in Periods 1 and 2; and RFB will be administered for 9 days in Period 2. There will be a washout period of 7 to 14 days between treatments in Period 1 Day 1 and Period 2 Day 1.

3.3. Protocol-Specific Discontinuation Criteria

Conduct of the study will be governed by participant withdrawal criteria and study-specific stopping criteria.

Study drug and/or study procedures may be discontinued in the following instances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree
- Unacceptable toxicity, as defined in Section 7.7, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the participant's best interest
- Participant request to discontinue for any reason
- Participant noncompliance
- Pregnancy during the study; refer to Appendix 11.3
- Discontinuation of the study at the request of Gilead Sciences (Gilead), a regulatory agency, or an institutional review board (IRB)
- Participant receives study drug(s) and experiences 1 or more AEs or laboratory abnormalities as follows:
  - Grade 2 or higher CRS, judged by the investigator as at least possibly related to study drug, OR
  - Grade 3 or higher TEAE (including new finding of splenomegaly, mucosal petechiae or purpura on physical examination) judged by the investigator as at least possibly related to study drug, OR
  - Grade 3 or higher confirmed laboratory abnormality (including a confirmed significant drop in platelets to $< 50 \times 10^9$/L and/or confirmed drop of 50% from baseline), unless there is a clear and obvious physiologic explanation for the events (eg, blood in urine occurring in a menstruating female, creatine kinase [CK] elevation after strenuous exercise, or triglyceride elevation that is nonfasting) judged by the investigators as at least possibly related to study drug, OR
  - A persistent (≥ 72 hours) Grade 2 or higher pyrexia considered related to study drug by the investigator, OR
  - Any SAE considered at least possibly related to study drug

3.3.1. Criteria for Early Discontinuation of an Individual Cohort

Study drug dosing of a cohort will be suspended when:

- 2 or more participants in a cohort experience a treatment-emergent, drug-related Grade 3 or higher clinical AE with the same medically similar preferred term (with the exception of headache or nausea)
- 2 or more participants in a cohort experience treatment-emergent, drug-related SAEs with the same medically similar preferred terms
- 2 or more participants in a cohort experience confirmed treatment-emergent, drug-related Grade 3 or higher clinically significant laboratory abnormality (with the exception of clinically insignificant Grade 3 or 4 cholesterol, triglyceride, glucose, CK elevations, or bilirubin abnormalities)
- The number and/or severity of AEs justifies discontinuation of the study
- The sponsor unilaterally requests it

If 2 or more participants in any cohort experience the same or similar SAE, Grade 3 or 4 TEAE or confirmed laboratory abnormality, unless there is a clear and obvious physiologic explanation for the events (eg, blood in urine due to menses, CK elevation after strenuous exercise, nonfasting triglyceride elevations), a review of all safety data generated in participants dosed to date will be initiated.

Decisions to reinitiate the cohort will be made in consultation with the sponsor and pending a safety review. In the event of a participant death, safety reports will be submitted to the appropriate regulatory authority for review and approval prior to reinitiating the cohort.

3.3.2. Loss to Follow-Up

Should the participant fail to return to the study site for a scheduled protocol-specified visit, the site will need to make multiple attempts by a combination of telephone calls and certified letters to contact the participant. The site must document all attempts to contact the participant. If a participant does not respond within 1 month after the missed protocol-specific visit, the participant will be considered lost to follow-up and no additional contact will be required.

3.4. Clinic Confinement

Following screening and admission assessments, eligible participants will be confined to the study site as follows:

- Cohort 1:

— In Period 1, participants will be confined beginning Day −1 until completion of assessments on Day 2.

— In Period 2, participants will be confined beginning on Day −1 until completion of assessments on Day 3.

— In Period 3, participants will be confined beginning on Day −1 until completion of assessments on Day 4.

- Cohort 2:

— In Period 1, participants will be confined beginning on Day −1 until completion of assessments on Day 2.

— In Period 2, participants will be confined beginning on Day −1 until completion of assessments on Day 7.

Participants may remain confined for a longer duration within each treatment period if this is preferred by the principal investigator (PI).

If a participant is experiencing signs and symptoms of CRS (see toxicity management Section 7.7), the participant will remain confined (for CRS symptoms of Grade 1) or immediately be transferred to a hospital or emergency department (for CRS symptoms of ≥ Grade 2) until symptoms resolve.

Participants will return 10 ± 3 days after the last dose of VES for an in-clinic follow-up visit.

3.5. Definitions for Time of Primary Endpoint and End of Study

3.5.1. Primary Endpoint

The date for the last participant last visit for the primary endpoint is the date of the last visit to perform assessments for the primary analysis.

3.5.2. End of Study

The end of this study will be the last participant's last observation (or visit).

3.6. Source Data

The source data for this study will be obtained from local laboratory and/or specialty laboratory (for PK and PD data).

4. PARTICIPANT POPULATION

4.1. Number of Participants and Participant Selection

Approximately 45 unique participants will be enrolled in the study. The study population will include male and nonpregnant, nonlactating female, virologically suppressed adults with HIV-1 on ART.

4.1.1. Participant Replacement

If necessary, replacement participants may be enrolled after discussion and approval from Gilead if participants do not complete all intensive PK procedures or the participant is considered nonevaluable. Replacement participants will not be enrolled for participants who discontinue the study due to study drug-related AEs.

4.2. Inclusion Criteria

Participants must meet all of the following inclusion criteria to be eligible for participation in this study:

1) Have the ability to understand and sign a written informed consent form (ICF), which must be obtained prior to initiation of study procedures
2) Males or nonpregnant, nonlactating females with HIV-1 aged at least 18 years
3) Be either a non-smoker/non-nicotine product user, or a smoker/nicotine product user who does not intend to change their pattern of use during the study
4) On an ART regimen for at least 6 consecutive months, with no change in the ART regimen within 2 months prior to screening. Permitted ART regimens are as follows:
   - Cohort 1: A regimen of (BIC, DTG, RAL, or DOR) plus NRTIs. Examples of acceptable regimens include BIC/emtricitabine/tenofovir, DTG/ABC/3TC, DTG/3TC, DTG + emtricitabine/tenofovir, or DOR/3TC/tenofovir
   - Cohort 2: A DTG-based regimen is required (DTG/ABC/3TC), (DTG/3TC), or (DTG + NRTIs)
5) Plasma HIV-1 RNA levels less than 50 copies/mL at screening.
6) Documented plasma HIV-1 RNA < 50 copies/mL for at least 6 months prior to the screening visit:
   a) Using all available viral load determinations for at least 6 consecutive months prior to the screening visit, HIV-1 RNA viral load must be below the limit of detection (50 copies/mL).
   b) A single isolated blip (defined as plasma HIV-1 RNA higher than the limit of quantification but < 200 copies/mL followed by a subsequent value below the limit of quantification) is allowed in the 6 months prior to screening.

7) Have normal hematologic function with an absolute neutrophil count greater than or equal to 1.5×10^9/L, platelets greater than or equal to 150×10^9/L; hemoglobin greater than or equal to 10.5 g/dL for females and greater than or equal to 11.5 g/dL for males

8) CD4 T cell count greater than or equal to 350 cells/μL

9) Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) less than or equal to 2.5 × ULN and total bilirubin less than or equal to 1.5 mg/dL, or normal direct bilirubin and creatinine less than or equal to 1.25 × ULN

10) Have a calculated creatinine clearance (CL_{cr}) of at least 60 mL/min (using the Cockcroft-Gault method {Cockcroft 1976}) based on serum creatinine and actual body weight as measured at screening and upon admission:

Assigned male at birth: $$\frac{(140 - \text{Age [years]}) \times (\text{Weight [kg]})}{72 \times (\text{Serum Creatinine [mg/dL]})} = CL_{cr}\ (\text{mL/min})$$

Assigned female at birth: $$\frac{(140 - \text{Age [years]}) \times (\text{Weight [kg]})}{72 \times (\text{Serum Creatinine [mg/dL]})} \times 0.85 = CL_{cr}\ (\text{mL/min})$$

11) Participants assigned female at birth and of childbearing potential and males at birth who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception as described in Appendix 11.3

12) Must be willing and able to comply with all study requirements and available to complete the study schedule of assessments

13) In the judgment of the investigator, be in good general health, based on review of the results from a screening visit (to include physical examination, measurement of vital signs, resting 12-lead electrocardiogram [ECG], and routine clinical laboratory testing), performed no more than 35 days prior to first study drug administration

4.3. Exclusion Criteria

Participants who meet *any* of the following exclusion criteria will not be enrolled in this study:

1) Have received any study drug within 30 days prior to study dosing

2) Participation in any other clinical study (including observation studies) without prior approval from the sponsor is prohibited while participating in this study

3) Have current alcohol or substance abuse judged by the investigator to potentially interfere with participant compliance or participant safety, or a positive drug or alcohol test at screening or baseline

4) Evidence of chronic hepatitis B virus (HBV) infection (defined as positive hepatitis B surface antigen [HBsAg] and/or positive HBV core antibody with positive reflex HBV DNA polymerase chain reaction [PCR]). Note: positive HBV core antibody with negative reflex HBV DNA PCR results are acceptable.

5) Evidence of active hepatitis C virus (HCV) infection (defined as positive hepatitis C antibody and HCV RNA above lower limit of quantitation). Note: positive anti-HCV antibody and negative HCV PCR results are acceptable.

6) Have poor venous access that limits phlebotomy

7) Acute febrile illness within 35 days prior to Day 1

8) Have been treated with systemic steroids, immunosuppressant therapies, or chemotherapeutic agents within 3 months prior to screening or is expected to receive these agents during the study (eg, corticosteroids, immunoglobulins, other immune- or cytokine-based therapies)

9) Received any vaccine or immunomodulatory medication within 4 weeks prior to screening. Elective vaccination (eg, flu shot, hepatitis A or B vaccine) during the course of the study will require prior approval from the sponsor

    a) COVID-19 vaccinations are allowed, with the requirement that they should not be administered within 7 ± 2 days of receiving VES

10) Have a history of any of the following:

- Significant serious skin disease, such as but not limited to rash, food allergy, eczema, psoriasis, or urticaria
- Significant drug sensitivity or drug allergy (such as anaphylaxis or hepatoxicity)
- Known hypersensitivity to the study drugs, their metabolites, or to formulation excipients (see Section 5)
- Autoimmune disease (eg, lupus erythematosus, rheumatoid arthritis, inflammatory, bowel disease, sarcoidosis, moderate or severe psoriasis)
- Significant cardiac disease (including history of myocardial infarction based on ECG and/or clinical history, any history of ventricular tachycardia, congestive heart failure, or dilated cardiomyopathy with left ventricular ejection fraction ≤ 40%); or a family history of long QT syndrome, or unexplained death in an otherwise healthy individual between the ages of 1 and 30 years
- Syncope, palpitations, or unexplained dizziness
- Implanted defibrillator or pacemaker
- Liver disease, including Gilbert syndrome
- Severe peptic ulcer disease requiring prolonged (≥ 6 months) medical treatment
- Medical or surgical treatment that permanently altered gastric absorption (eg, gastric or intestinal surgery). A history of cholecystectomy is not exclusionary

11) Have any serious or active medical or psychiatric illness (including depression) that, in the opinion of the investigator, would interfere with participant treatment, assessment, or compliance with the protocol. This would include renal, cardiac, hematological, hepatic, pulmonary (including chronic asthma), endocrine (including diabetes), central nervous, gastrointestinal (including an ulcer), vascular, metabolic (thyroid disorders, adrenal disease), immunodeficiency disorders other than HIV-1 infection, active infection, or malignancy that are clinically significant or requiring treatment

12) Requirement for ongoing therapy with or use (within 14 days prior to study drug administration) of any prohibited medications listed in Section 5.7.1

13) For Cohort 1, participant with CYP2C19 genotype of CYP2C19*2/*2, CYP2C19*2/*3, or CYP2C19*3/*3

14) Have any of the following ECG abnormalities at screening: QRS more than 120 milliseconds; heart rate less than 45 beats per minute; second or third degree heart block; prolongation of QTcF interval (eg, a prolongation of the QTcF interval of greater than 450 milliseconds for males and more than 470 milliseconds for females); or PR interval more than 200 milliseconds

5. STUDY INTERVENTIONS AND CONCOMITANT MEDICATIONS

5.1. Enrollment, Blinding, and Treatment Code Access

5.1.1. Enrollment

At screening, study participants will be assigned a screening number at the time of consent and they will be assigned to Cohort 1 or 2. Once eligibility has been confirmed following completion of the admission study procedures, participants will be enrolled and assigned a unique participant number using an interactive response technology.

All screening and admission (Day −1) tests and procedures must be completed and reviewed by the investigator prior to the administration of the first dose of study drug on Day 1. It is the responsibility of the investigator to ensure that the participant is eligible for the study prior to enrollment. Once a participant number has been assigned to a participant, it will not be reassigned to another participant. If necessary, replacement participants may be enrolled after discussion and approval from the sponsor. A new unique participant number will be assigned to the replacement participant.

5.1.2. Blinding

Blinding to treatment assignments or data will not be performed in this study.

5.2. Description and Handling of Vesatolimod

5.2.1. Formulation

Vesatolimod 2 mg strength tablets are round, biconvex, plain-faced, white, and film-coated. Vesatolimod tablets contain the following inactive ingredients: lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

5.2.2. Packaging and Labeling

Vesatolimod tablets are packaged in white, high-density polyethylene bottles. Each bottle contains 3 tablets of 2 mg strength, silica gel desiccant, and polyester packing material. Each bottle is capped with a child-resistant polypropylene screw cap fitted with an induction-sealed, aluminum-faced liner.

Study drugs to be distributed to US centers will be labeled to meet applicable requirements of the US Food and Drug Adminstration (FDA) and/or other local regulations.

5.2.3. Storage and Handling

Vesatolimod tablets should be stored at controlled room temperature of 25 °C (77 °F); excursions are permitted between 15 °C and 30 °C (59 °F and 86 °F). Storage conditions are specified on the label. Bottles are to be kept tightly closed.

Until dispensed to the participants, the study drug should be stored in a securely locked area, accessible only to authorized site personnel. To ensure proper product identification, the drug products should be stored in the containers in which they are supplied. Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling the study drug.

If the 3 tablets in a bottle are not administered at the same time, the tablets in an opened bottle are consumed first before opening a new bottle to minimize exposure to moisture. The cap of an opened bottle should be closed during storage.

5.3. Description and Handling of Commercially Available Drugs

Commercial products of COBI, VOR, and RFB will be used for the study. Cobicistat will be provided as 150 mg tablets, VOR will be provided as 200 mg tablets, and RFB will be provided as 150 mg capsules. Further information regarding storage and handling are available in the prescribing information for these commercial products.

5.4. Dosage and Administration

Following completion of screening and admission assessments, eligible participants will receive treatments orally according to the cohort to which they are assigned as outlined in Table 5.

Table 5. Treatments to be Administered in Cohorts 1 and 2

Cohort	Period 1	Period 2	Period 3
1	VES 2 mg on Day 1	COBI 150 mg once daily on Days 1 to 5 and a single dose of VES 2 mg on Day 2 within 1 hour after COBI dosing	VOR 400 mg twice daily on Day 1, then VOR 200 mg twice daily on Days 2 to 6, and a single dose of VES 2 mg on Day 3 within 1 hour after the morning VOR dose
2	VES 6 mg on Day 1	RFB 300 mg once daily on Days 1 to 9 and a single dose of VES 6 mg on Day 6 within 1 hour after RFB dosing	NA

COBI = cobicistat; NA = not applicable; RFB = rifabutin; VES = vesatolimod; VOR = voriconazole
Vesatolimod tablets are 2 mg each.

5.5. Fasting and Meals

All study treatments will be administered orally at approximately the same time each day relative to VES dosing in each period (± 1 hour) with 240 mL of water. All VES doses will be administered in the morning following an overnight fast (no food or drinks except water) for at least 8 hours. Participants will continue to fast until after collection of the 4-hour PK sample, relative to VES dosing. Additionally, participants will be restricted from water consumption from 2 hours before through 2 hours after VES dosing, except for the 240 mL given with the study drug. All COBI, VOR, and RFB doses will be administered on an empty stomach, defined as no food or drinks, except water, for at least 2 hours before and 2 hours after dosing.

5.6. Dispensing, Accountability, and Disposal or Return of Study Drug

The investigator (or designee, eg, study site pharmacist) will acknowledge receipt of the study drugs (after reviewing the shipment's content and condition) from Gilead (or designee). The investigator (or designee) will maintain an accurate inventory of all study drugs. Each dose of the study drugs administered at the study site will be administered by qualified study site staff. The dose of study drugs administered to participants in the clinic under the supervision of staff will be accurately recorded on the Study Drug Accountability form provided by Gilead (or on equivalent documentation maintained by the study site), which indicates the date and quantity of each dosage formulation dispensed to individual participants.

Gilead recommends that used and unused study drugs should be destroyed at the site. If the site has an appropriate standard operating procedure for study drug destruction as determined by Gilead, the site may destroy used (empty or partially empty) and unused study drugs in accordance with that site's approved procedural documents. A copy of the site's approved procedural document will be obtained for the electronic trial master file. If study drugs are destroyed on site, the investigator must maintain accurate records for all study drugs destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drug. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be returned to Gilead.

If the site does not have an appropriate procedural document for study drug destruction, used and unused study drugs are to be sent to the designated disposal facility for destruction. The study monitor will provide instructions for return.

The study monitor will review study drug supplies and associated records at periodic intervals.

5.7. Concomitant Medications and Other Protocol Restrictions

5.7.1. Concomitant Medications

5.7.1.1. Permitted Medications

This section describes permitted medications for use during the study. If participants are taking other medications, they must be reviewed with the sponsor prior to enrollment. In addition, if medications, other than the stated permitted medications, are needed during the study, they should be reviewed with the sponsor as soon as possible.

5.7.1.1.1. ART

See Inclusion Criteria (Section 4.2).

5.7.1.1.2. Contraception

See Pregnancy Precautions, Definition of Childbearing Potential, and Contraceptive Requirements (Appendix 11.3).

5.7.1.1.3. Other Permitted Medications

Vitamins, acetaminophen (paracetamol), aspirin, ibuprofen, antacids, famotidine, nizatidine, dexlansoprazole, lansoprazole, pantoprazole, rabeprazole, and short-term use of topical steroid (eg, hydrocortisone) and antihistamine (eg, diphenhydramine) creams are allowed during the study period.

Participants assigned female at birth taking hormonal contraception (oral or implant) may continue to use these medications during the study but must not rely solely on these methods for contraception (see Appendix 11.3 for additional details on contraception requirements).

There are no substantial safety data regarding the concomitant administration of the COVID-19 vaccines and VES. Participants are allowed to receive the COVID-19 vaccine, and study visits should continue as planned if vaccination occurs while the participant is on the study. A COVID-19 vaccination should not be administered within 7 ± 2 days of receiving VES.

5.7.1.2. Prohibited Medications

If participants are taking medications, other than the stated permitted medications (Section 5.7.1.1), they should be reviewed with the sponsor prior to enrollment. In addition, if a participant requires a new medication, other than the stated permitted medications, they should be reviewed with the sponsor as soon as possible.

The following types of medications and herbal supplements are prohibited from within 14 days prior to enrollment and through the follow-up visit.

- Medications that could increase VES exposure through inhibition of CYP3A, P-gp, or BCRP.
- Medications that could decrease VES exposure through induction of CYP3A, P-gp, or BCRP.
- Medications that prolong the QT interval (applicable to Cohort 1 Period 3, see Table 6). Opioids (excluding methadone) are permitted after discussion with and approval from the Gilead medical monitor.
- Any and all illegal or illicit drug use, including use of prescription drugs outside the care of the prescribing physician.
- Recreational or medical cannabinoids or derivatives.

Table 6. Common Medications That Could Prolong QT Interval

Antibiotics	Antifungals	Antivirals	Antianginals	Antihistaminics	Antipsychotics
Quinolones	Azoles	Lopinavir	Ranolazine	Fexofenadine	Aripiprazole
Macrolides		Nelfinavir	Ivabradine	Astemizole	Chlorpromazine
Telavancin		Saquinavir		Diphenhydramine	Haloperidol
Metronidazole		Amantadine			Droperidol
Pentamidine		Atazanavir			Olanzapine
					Risperidone
					Thioridazine
Antidepressants	**Antiemetics**	**Analgesics**	**CNS Stimulant**	**Antineoplastic Agents**	**Sedatives**
Amitriptyline	Metoclopramide	Methadone	Dexamphetamine	Arsenic trioxide	Dexmedetomidine
Amoxapine	Domperidone		Amphetamine	Bosutinib	Chloral hydrate
Citalopram	Dolasetron		Methylphenidate	Dasatinib	
Doxepin	Ondansetron			Dabrafenib	
Escitalopram	Granisetron			Eribulin	
Imipramine				Nilotinib	
Nortriptyline					

CNS = central nervous system

Immunomodulators are prohibited from 28 days prior to screening through the follow-up visit.

Systemic steroids, immunosuppressant therapies, or chemotherapeutic agents are prohibited from 3 months prior to screening through the follow-up visit.

Prohibited medications are provided in Table 7. Participants who are taking any medications not specifically included as either permitted medications (Section 5.7.1.1) or prohibited medications (Table 7) should have their medications reviewed by the sponsor prior to enrollment.

Table 7. Prohibited Medications

Drug Class	Agent(s) Disallowed
Acetyl-coenzyme A acetyltransferase inhibitor	Avasimibe
Angiotensin-converting enzyme inhibitor	Captopril
Analeptic	Modafinil, lomitapide
Angiotensin II inhibitor	Telmisartan
Anti-androgens	Apalutamide, enzalutamide
Anti-anginal	Ranolazine
Anti-arrhythmics	Amiodarone, dronedarone, quinidine
Antibiotics	Azithromycin, clarithromycin, erythromycin, nafcillin, telithromycin
Anticonvulsants	Carbamazepine, phenytoin, phenobarbital, oxcarbazepine, cenobamate
Antidepressants	Fluvoxamine, nefazodone, venlafaxine, ziprasidone, paroxetine
Antidiabetic	Pioglitazone
Antiepileptic	Divalproex
Antiemetics	Aprepitant, casopitant
Antifungals	Caspofungin, ketoconazole, itraconazole, voriconazole, posaconazole, fluconazole, clotrimazole
Antimigraine	Rimegepant
Antimycobacterials	Rifampin, rifapentine
Beta-blockers	Carvedilol, talinolol
Calcium channel blockers	Amlodipine, diltiazem, felodipine mibefradil, nicardipine, nifedipine, nitrendipine, verapamil
Diuretic	Conivaptan
Endothelin receptor antagonist	Bosentan
Gonadotropin-releasing hormone receptor antagonist	Elagolix
Herbal/natural supplements	St John’s wort, echinacea, gingko, milk thistle, Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)
Histamine-2 receptor antagonists	Cimetidine, ranitidine
3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor	Atorvastatin
Immunosuppressants	Cyclosporine, rapamycin, sirolimus, tacrolimus
Proton pump inhibitors	Esomeprazole, omeprazole
Systemic corticosteroids	All agents, including dexamethasone
Systemic chemotherapeutic (antineoplastic) agents	All agents

5.7.2. Other Protocol Restrictions

- Participants will be required to refrain from the consumption of beverages containing alcohol products 72 hours prior to the first dose of study drug and during the course of the study through the follow-up visit

- Participants who are smokers/nicotine product users will be required to not change their pattern of use throughout the course of the study

- Participants will be required to refrain from consumption of grapefruit juice, grapefruits, and Seville orange juice 72 hours prior to the first dose of study drug and during the course of the study through the end of study drug administration period

- While confined at the study site, tea, coffee, chocolate, and other foods and beverages containing caffeine and other methyl xanthines will be prohibited on each dosing day. At all other times, caffeine-containing beverages and food may be served or withheld in accordance with normal practice at the site. Caffeine-containing beverages and food will not be restricted while participants are outside of the clinic

- Participants will be encouraged to avoid strenuous or prolonged exercise, as well as saunas, steam baths, and sunbathing or other prolonged ultraviolet exposure (eg, in a tanning salon) from the screening evaluation until completion of the follow-up visit, as these activities are known to affect certain clinical laboratory test parameters (eg, CK) and will provide false indicators of a potentially treatment-related toxicity

Upon every admission to the clinic, each participant will be questioned as to their compliance with the above protocol restrictions. If a participant is unable to comply with any of the restrictions described above, the participant's continued participation in the study will be reevaluated by the investigator in consultation with the sponsor.

6. STUDY ASSESSMENTS

The study procedures to be conducted for each participant enrolled in the study are presented in tabular form in Table 1 through Table 3 and detailed below.

Any deviation from protocol procedures should be noted in the participant's clinical chart and appropriate electronic case report forms (eCRFs). In addition, the sponsor should be promptly notified of any protocol deviations.

The study site will not initiate dosing until the following have all been met:

- The IRB or other applicable regulatory agencies have reviewed and approved the study and the informed consent document
- All requested regulatory documents have been submitted to and approved by Gilead
- A master services agreement and/or study agreement is executed
- The study initiation meeting has been conducted by Gilead (or designee)

The initiation meeting will include but is not limited to a review of the protocol, the IB, study drug(s), and investigator responsibilities.

Documentation of the personally signed and dated ICF for each participant, using the study-specific, IRB-approved ICF, is required before initiating the screening process.

6.1. Informed Consent

Written informed consent must be obtained from each participant before initiation of any screening procedure. After a participant has provided informed consent, the investigator and other study personnel will determine if the participant is eligible for participation in the study (Section 6.3.2).

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6.2. Participant Enrollment and Treatment Assignment

Entry into screening does not guarantee enrollment into the study. In order to manage the total study enrollment, Gilead, at its sole discretion, may suspend screening and/or enrollment at any site or study-wide at any time.

It is the responsibility of the investigator to ensure that participants are eligible to participate in the study prior to enrollment and continue to remain eligible throughout the study.

Once the ICF has been obtained, all screening and admission tests and assessments have been assessed, and study eligibility has been confirmed, participants will be enrolled to receive study drug on Day 1.

Participants will receive the study treatments as described in Section 5.4.

6.3. Instructions for Study Procedures

6.3.1. Adverse Events

From the time informed consent is obtained through the first administration of study drug, record all SAEs, as well as any AEs related to protocol-required procedures on the AE eCRF. All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history, are to be considered medical history. After study drug administration, report all AEs and SAEs (including washout periods [Participants should inform the site of any AE during the washout period]). Evaluation of AEs will occur at the visits shown in Table 1 through Table 3. See Section 7 for additional details.

6.3.2. Screening Assessments

Screening laboratory assessments may be repeated once within 35 days prior to administration of study drug for exclusionary laboratory values if, in the PI's opinion, 1 of the following are met: there is reason to believe the retest value will be within accepted parameters, if the initial value was deemed to be inaccurate or inconsistent with the participant's previous result(s), if the initial value was generated in error (eg, mishandled sample), or there is another relevant extenuating circumstance. In any instance, the site should obtain approval from Gilead prior to repeating the laboratory assessment.

A sufficient number of participants will be screened to identify the planned number of participants for enrollment.

Participants should be instructed to fast (no food or drink, except water), starting from midnight (00:00) or earlier, as appropriate, on the evening prior to the screening visit to ensure an approximate 8-hour fast prior to the fasted blood sample collection the next morning.

The screening assessment will include a review of the inclusion/exclusion criteria and completion of all screening procedures as outlined in Table 1 and Table 3 and described in the following text.

Eligible participants meeting all of the inclusion criteria and none of the exclusion criteria will be instructed on all protocol requirements, including the restrictions on concomitant medication usage and other substances as well as consumption of food or beverages containing alcohol, caffeine, or xanthine. Participants will be asked to arrive at the study site on Day −1 for admission assessments.

6.3.3. Admission Assessments

6.3.3.1. Admission

Participants should be instructed to fast (no food or drink, except water), starting from midnight (00:00) or earlier, as appropriate, on the evening prior to the admission visit to ensure an approximate 8-hour fast prior to the fasted blood sample collection.

Participants meeting all eligibility criteria following the screening evaluation will return to the site for admission assessments on Day −1. The admission evaluations and/or procedures are outlined in Table 1 and Table 3.

Note: On Day −1 (admission), 2 sets of safety laboratory results for hematology, chemistry, urinalysis, urine drug, and alcohol assessments will be collected upon study center admission. One will be sent to the central laboratory and the other will be sent to the site's local laboratory to obtain results in time for enrollment on Day 1.

If a study center cannot perform a urine alcohol test or receive results from the local laboratory in time for enrollment on Day 1, then an alcohol breathalyzer test is acceptable.

Prior to dosing on Day 1, the results of the clinical and laboratory evaluations (as described in Table 1 and Table 3) must be reviewed by the investigator to confirm the continued eligibility of each participant to participate in the study. At the time of enrollment, participants will be assigned a participant number as described in Section 5.1.1. Participants will remain confined to the study clinic for the duration as described in Section 6.3.3.2 and Table 1 through Table 3.

6.3.3.2. Clinic Confinement

6.3.3.2.1. Cohort 1 (With or Without COBI or VOR)

In Period 1, participants will be confined beginning Day −1 until completion of assessments on Day 2. In Period 2, participants will be confined beginning on Day −1 until completion of assessments on Day 3. In Period 3, participants will be confined beginning on Day −1 until completion of assessments on Day 4.

6.3.3.2.2. Cohort 2 (With or Without RFB)

In Period 1, participants will be confined beginning on Day −1 until completion of assessments on Day 2. In Period 2, participants will be confined beginning on Day −1 until completion of assessments on Day 7.

6.3.4. Check-in Assessments

Following completion of screening and Day −1 assessments, eligible participants will be assigned a participant number and receive study treatments as described in Section 5.4.

6.3.5. Treatment Assessments

Study procedures and assessments are outlined in Table 1 through Table 3.

6.3.6. Pharmacokinetic Assessments

6.3.6.1. Plasma PK Collection

Plasma concentrations of VES will be determined and PK parameters estimated. Plasma concentration of COBI, VOR, and RFB may be determined and PK parameters may be estimated.

Intensive PK sampling time points and time windows allowed are shown in Table 8.

Table 8. PK Sampling Time Points and Time Windows

Day	Nominal Hour (Min)	Time Window
1	0.25 (15 min)	± 3 min
	0.5 (30 min)	± 5 min
	1 (60 min)	± 10 min
	1.5	± 10 min
	2	± 10 min
	2.5	± 10 min
	3	± 10 min
	4	± 10 min
	6	± 30 min
	8	± 30 min
	12	± 30 min
2	24	± 30 min
3	48	± 30 min
4	72	± 30 min
5	96	± 30 min

Clinical staff should make every effort to ensure that the sampling time is as close as possible to the nominal time. The exact time and date of the blood draw must be recorded in the electronic data capture (EDC) system.

6.3.6.2. Blood Collection for Pharmacogenetic Assessments

A blood specimen will be collected for the extraction of DNA to test for polymorphisms of genes that could regulate or be involved in the disposition or effects of VES, including TLR7 and BCRP (also known as the adenosine triphosphate-binding cassette transporter G2; gene symbol *ABCG2*). The pharmacogenetics sample should be collected on Day 1 in Period 1, before administration of the first dose of study drug, but may be collected at any time during the study, if necessary.

For Cohort 1, a sample for CYP2C19 genotyping will be collected during screening as part of the inclusion/exclusion criteria.

6.3.7. Biomarker Testing

6.3.7.1. Biomarker Samples to Address the Study Objectives

The following biological specimens will be collected from all participants who have provided consent to participate in this study and may be used to evaluate the association of systemic and/or tissue-based biomarkers with study drug response (including efficacy and/or AEs) and dosage selection, and to better understand the biological pathways, biology of HIV or related diseases and/or the validation of a companion diagnostic for HIV cure. Because biomarker science is a rapidly evolving area of investigation, and AEs in particular are difficult to predict, it may not be possible to specify prospectively all tests that may be done on the specimens provided. The specific analyses will include but may not be limited to the biomarkers and assays listed below. The testing outlined below is based upon the current state of scientific knowledge. It may be modified during or after the end of study to remove tests no longer indicated and/or to add new tests based upon new state of the art knowledge.

The following samples will be collected relative to dosing at the time points specified in Table 1 through Table 3:

- Serum biomarkers for PD and safety assessments, which may include (but not limited to): IFN-α, interleukin (IL)-1 receptor antagonist, interferon gamma inducible protein-10, interferon-inducible T cell alpha chemoattractant, interferon-gamma, IL-1 beta, IL-6, tumor necrosis factor alpha, and C-reactive protein
- Whole blood for ISG mRNA expression (including, but not limited to, MX1, ISG15, OAS1)
- Whole blood for immune cell phenotyping
- Whole blood for TruCulture cytokine response

Clinical staff should make every effort to ensure that the sampling time is as close as possible to the nominal time. The exact time and date of the blood draw must be recorded in the EDC system.

Samples collected for biomarker assessments will be destroyed no later than 15 years after the end of study or per country requirements (Section 9.1.4).

CCI [redacted] and/or diagnostic assays and establish the performance characteristics of these assays.

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6.4. Safety Assessments

Safety will be evaluated throughout the study. All safety assessments will be completed predose unless otherwise specified as in the schedule of assessments in Table 1 through Table 3.

6.4.1. Electrocardiogram Assessment

Participants should rest quietly in the supine position for a minimum of 5 minutes prior to each scheduled ECG acquisition and should remain in that position until the recording is complete.

There should be no environmental distractions (including TV, radio, video games, and conversation) while the participants are resting prior to and during the recordings. Electrocardiograms will be recorded using the site's standard ECG equipment. All ECGs will be obtained using instruments that analyze data using the same algorithms and produce the same data for interpretation. Electrode placement will be performed according to the method of Wilson, Goldberger, and Einthoven with a check to confirm that the aVR lead is not inverted.

The investigator or other qualified individuals at the study site will review ECGs to assess for changes in ECG intervals and morphology as compared with pretreatment ECGs. The ECG interval measurements output by the machine will be used for bedside safety monitoring.

Collection of additional ECGs for routine safety monitoring at additional time points or days is at the discretion of the investigator based on GCP.

6.4.2. Physical Examination

Physical examinations conducted throughout the study will be a complete physical examination or a symptom-driven physical examination, as outlined in Table 1 through Table 3. The complete physical examination conducted at screening will also include the following assessments:

- Review medical history, including history of allergies, prior and current use of nicotine or nicotine-containing products, alcohol and illegal drug use, and prior (within 30 days) and current medication use

6.4.3. Vital Signs

Vital sign measurements include blood pressure, heart rate, oxygen saturation, and body temperature and should be taken once participants have been seated or in the supine position. Participant position for measurement should be kept consistent throughout the study. Refer to Table 1 through Table 3 for vital signs collection time points.

6.4.4. Body Mass Index

Height and weight will be collected at screening for calculation of body mass index (BMI).

6.4.5. Clinical Laboratory Tests/Assessments

Blood and urine samples for safety evaluations will be collected throughout the study as outlined in Table 1 through Table 3.

6.4.5.1. Blood Sampling

Blood samples will be collected for the following laboratory analyses:

- Hematology: Hematocrit, hemoglobin, platelet count, red blood cell count, white blood cell count with differential (absolute and percentage), including lymphocytes, monocytes, neutrophils, eosinophils, basophils, and mean corpuscular volume
- Coagulation panel (*screening only*): prothrombin time, partial thromboplastin time, and international normalized ratio
- Chemistry (fasting): alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, total protein, albumin, lactic acid dehydrogenase, CK, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine (see Section 6.4.6), glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in participants with total amylase greater than 1.5 × ULN)
- Serum pregnancy test (participants assigned female at birth of childbearing potential only)
- Follicle-stimulating hormone testing (*screening only*): participants assigned female at birth who are younger than 54 years, not on hormonal contraception, and who have stopped menstruating for at least 12 months but do not have documentation of ovarian hormonal failure
- HIV-1 viral load at screening and on Day −1 of Period 2 and Period 3 in Cohort 1, and screening and Day −1 of Period 2 in Cohort 2
- HBV and HCV testing (*screening only*)

6.4.5.2. Urine Samples

Urine samples will be collected for urinalysis and alcohol and drug screen assessments, which include alcohol, amphetamines, barbiturates, benzodiazepines, cocaine, marijuana, 3,4-methlenediozymethamphetamine, methadone, opiates, phencyclidine, and propoxyphene.

6.4.6. Creatinine Clearance

Serum creatinine and weight will be collected at screening and upon admission to calculate CL_{cr} for inclusion criteria. Weight collected at admission will be used to calculate CL_{cr} from Day 5 until the end of study in each cohort. Serum creatinine to calculate CL_{cr} will be collected at later time points as outlined in Table 1 through Table 3.

6.4.7. Concomitant Medications/Protocol Restrictions

Review of concomitant medications, and review of protocol restrictions will occur at the times shown in Table 1 through Table 3. See Sections 4.3 and 5.7.1 for more information about concomitant medications.

6.5. Posttreatment Assessments

All participants will return 10 days ± 3 days after last dose of VES for an in-clinic follow-up visit. For participants assigned female at birth of childbearing potential in Cohort 2 only, an at-home urine pregnancy test will be completed 10 days after the last dose of RFB . Participants will be contacted by telephone to report at-home pregnancy test results. Study procedures and assessments are outlined in Table 2 and Table 3.

6.6. Assessments for Early Discontinuation From Study Intervention or From the Study

If a participant discontinues study treatment dosing (see Sections 3.3), for example as a result of an AE, every attempt should be made to keep the participant and continue to perform procedures for stabilization per the investigator. Evaluations indicating abnormal results believed to be possibly or probably related to study drug at the early termination (ET) visit should be repeated weekly or as often as deemed appropriate by the investigator until the abnormality resolves, returns to baseline visit levels, or is otherwise explained.

6.6.1. Assessments for End of Study

A participant who completes the study will have an end of study visit for assessments and procedures specified in Table 2 and Table 3. If the participant withdraws consent from the study, the ET evaluations and/or procedures outlined in Table 2 and Table 3 should be performed within 72 hours of permanently discontinuing the study.

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7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events and Serious Adverse Events

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study participant administered a study drug that does not necessarily have a causal relationship with the treatment. An AE can, therefore, be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a study drug, whether or not considered related to the study drug. Adverse events may also include pretreatment or posttreatment complications that occur as a result of protocol-specified procedures, or special situations (Section 7.1.3).

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and must be reported
- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.1.3)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the ICF is signed and not related to a protocol-associated procedure is not an AE but rather considered to be preexisting and should be documented medical history

Preexisting events that increase in severity or change in nature after study drug initiation or during or as a consequence of participation in the clinical study will also be considered AEs.

7.1.2. Serious Adverse Events

An SAE is defined as an event that, at any dose, results in the following:

- Death
- A life-threatening situation (Note: 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 that hypothetically might have caused death if it were more severe)
- Inpatient hospitalization or prolongation of existing hospitalization

- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction; such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent 1 of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse

7.1.3. Study Drugs and Gilead Concomitant Therapy Special Situation Reports

Special situations reports (SSRs) include all reports of medication error, abuse, misuse, overdose, occupational exposure, drug interactions, exposure via breastfeeding, unexpected benefit, transmission of infectious agents via the product, counterfeit of falsified medicine, and pregnancy regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, preparation for administration or administration of a study drug while the medication is in the control of a health care professional, patient, or consumer. Medication errors may be classified as a medication error without an AE, which includes situations of missed dose, medication error with an AE, intercepted medication error, or potential medication error.

Abuse is defined as persistent or sporadic intentional excessive use of a study drug by a participant.

Misuse is defined as any intentional and inappropriate use of a study drug that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a study drug given per administration or cumulatively that is above the maximum recommended dose as per protocol or in the product labeling (as it applies to the daily dose of the participant in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the participant has taken the excess dose(s). Overdose cannot be established when the participant cannot account for the discrepancy, except in cases in which the investigator has reason to suspect that the participant has taken the additional dose(s).

Occupational exposure is defined as exposure to a study drug as a result of one’s professional or nonprofessional occupation.

Drug interaction is defined as any drug/drug, drug/food, or drug/device interaction.

Unexpected benefit is defined as an unintended therapeutic effect where the results are judged to be desirable and beneficial.

Transmission of infectious agents is defined as any suspected transmission of an infected agent through a Gilead study drug.

Counterfeit or falsified medicine is defined as any study drug with a false representation of (a) its identity, (b) its source, or (c) its history.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship for each study drug using clinical judgment and the following considerations:

- **No:** Evidence exists that the AE has an etiology other than the study drug. For SAEs, an alternative causality must be provided (eg, preexisting condition, underlying disease, intercurrent illness, concomitant medication)
- **Yes:** There is reasonable possibility that the AE may have been caused by the study drug

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No:** Evidence exists that the AE has an etiology other than the study procedure
- **Yes:** The AE occurred as a result of protocol procedures (eg, venipuncture)

7.2.2. Assessment of Severity

The severity of AEs will be graded using the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities, Antiviral Toxicity Grading Scale, Version 01 April 2015 (Appendix 11.5). For each episode, the highest grade attained should be reported as defined in the Antiviral Toxicity Grading Scale (Appendix 11.5). The Common Terminology Criteria for Adverse Events (CTCAE) v5.0 grading scale will be used to grade CRS AEs.

7.3. Investigator Reporting Requirements and Instructions

7.3.1. Requirements for Collection Prior to Study Drug Initiation

After informed consent, but prior to initiation of study medication, the following types of events must be reported on the applicable forms: all SAEs (paper case report forms [CRFs]) and any AEs related to protocol-mandated procedures (eCRFs).

7.3.2. Adverse Events

Following initiation of study treatment, all AEs, regardless of cause or relationship, throughout the duration of the study, including the protocol-required posttreatment follow-up period, must be reported to the CRF database as instructed. Following initiation of study treatment, collect all AEs, regardless of cause or relationship, until 30 days after follow-up and report the AEs on the CRF as instructed.

All AEs and clinically significant laboratory abnormalities should be followed up until resolution or until the AE is stable, if possible. Gilead may request that certain AEs be followed beyond the protocol-defined follow-up period.

7.3.3. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occurs after the participant first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the posttreatment follow-up visit, must be reported on the applicable CRFs and to Gilead Patient Safety (PS) as instructed below in this section. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Any SAEs and deaths that occur throughout the duration of the study including the protocol-defined follow-up period, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol-defined follow-up period; however, if an investigator learns of any SAEs that occur after the protocol-defined follow-up period has concluded and the event is deemed relevant to the use of the study drug, the investigator should promptly document and report the event to Gilead PS.

Instructions for reporting SAEs are described in Section 7.4.1.

7.3.4. Study Drug Special Situations Reports

All study drug SSRs that occur from study drug initiation and throughout the duration of the study, including the posttreatment follow-up visit, must be reported to Gilead PS (Section 7.4.2). Adverse events and SAEs resulting from SSRs must be reported in accordance to the AE and SAE reporting guidance (Section 7.3).

7.3.5. Concomitant Therapy Reports

7.3.5.1. Gilead Concomitant Therapy Special Situations Report

Special situations reports involving a Gilead concomitant therapy (not considered study drug), that occurs after the participant first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the posttreatment follow-up visit, must be reported to Gilead PS utilizing the paper SSR (Section 7.4.2.2).

7.3.5.2. Non-Gilead Concomitant Therapy Report

Special situations involving non-Gilead concomitant medications do not need to be reported on the SSR form; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be reported on the AE form.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

All clinical sequelae in relation to these SSRs will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

7.4. Reporting Process for Serious Adverse Events and Special Situations Reports

7.4.1. Serious Adverse Event Reporting Process

For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be transmitted by email or fax when requested and applicable. Transmission of such documents should occur without personal participant identification, maintaining the traceability of a document to the participant identifiers.

Additional information may be requested to ensure the timely completion of accurate safety reports.

Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the participant's eCRF and the SAE narrative section of the Safety Report Form eCRF.

7.4.1.1. Paper Serious Adverse Event Reporting Process

All SAEs will be recorded on the SAE report form and transmitted by emailing or faxing the report form within 24 hours of the investigator's knowledge of the event to the attention of Gilead PS from ICF signature throughout the duration of the study, including the protocol-required posttreatment follow-up period. Additionally, the SAE must be captured on the applicable CRF.

Gilead PS	Email: PPD or Fax: PPD

7.4.2. Special Situations Reporting Process

7.4.2.1. Paper Special Situations Reporting Process for Study Drug

All SSRs will be recorded on the SSR form and transmitted by emailing or faxing the report form within 24 hours of the investigator's knowledge of the event to the attention of Gilead PS from study drug initiation throughout the duration of the study, including the protocol-required posttreatment follow-up period.

Gilead PS

Email: PPD
or
Fax: PPD

7.4.2.2. Reporting Process for Gilead Concomitant Medications

Special situations that involve Gilead concomitant medications that are not considered study drug must be reported within 24 hours of the investigator's knowledge of the event to Gilead PS utilizing the paper SSR form to:

Gilead PS

Email: PPD
or
Fax: PPD

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

Special situations involving non-Gilead concomitant medications do not need to be reported on the SSR form; however, special situations that result in AEs due to a non-Gilead concomitant medication, must be reported as an AE.

7.4.2.3. Pregnancy Reporting Process

The investigator should report pregnancies identified after initiation of study drug and throughout the study, including the protocol-required posttreatment follow-up period in participants and/or pregnancies in partners resulting from exposure to sperm from a participant in the study period in which contraceptive measures are needed. Pregnancies should be reported to Gilead PS using the pregnancy report form within 24 hours of becoming aware of the pregnancy. Contact details for transmitting the pregnancy report form are as follows:

Gilead PS

Email: PPD
or
Fax: PPD

The pregnancy itself is not considered an AE, nor is an induced elective abortion to terminate a pregnancy without medical reasons.

All other premature terminations of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE, as described in Section 7.4.1. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 7.4.1. Furthermore, any SAE occurring as an adverse pregnancy outcome poststudy must be reported to the Gilead PS.

The participant should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome of the pregnancy/partner pregnancy should be reported to Gilead PS using the pregnancy outcome report form. If the end of the pregnancy/partner pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PS. Gilead PS contact information is as follows: email: PPD and fax: PPD.

Refer to Appendix 11.3 for Pregnancy Precautions, Definition for Childbearing Potential, and Contraceptive Requirements.

7.5. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable FDA CFR, the European Union (EU) Clinical Trials Directive (2001/20/EC)/EU Regulation 536/2014 and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, which may be in the form of line-listings, serious adverse drug reactions, or suspected unexpected serious adverse reactions (SUSARs). In accordance with the European Union Clinical Trials Directive (2001/20/EC)/EU Regulation 536/2014, Gilead or a specified designee will notify worldwide regulatory agencies of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the IB or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study drug. The investigator should notify the IRB of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.6. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not to be recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, urinalysis) that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, ECG, X-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2, respectively. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia) not the laboratory result (ie, decreased hemoglobin).

Severity should be recorded and graded according to the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities, Antiviral Toxicity Grading Scale, Version 01, April 2015, and the CTCAE v5.0 grading scale for CRS (Appendix 11.5 and Section 7.7, respectively) Toxicity Grading Scales (Section 7.2.2). For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.7. Toxicity Management

All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in Appendix 11.5, and as outlined below.

Cytokine Release Syndrome

After VES dosing, Grade 1 CRS, with influenza-like symptoms such as fever, fatigue, chills, myalgia, or headache without more severe manifestations such as changes in blood pressure or oxygen saturation, may be managed with supportive care (eg, paracetamol for myalgia or fever). If a participant experiences Grade 1 CRS, they will remain confined until symptoms resolve. For any Grade 2 or higher CRS, including hypotension and/or hypoxia, the participant will be immediately transferred to a hospital or emergency department for management in a monitored setting until symptoms resolve. Administration of steroids, intravenous fluid for hypotension, and supplemental oxygen for hypoxia should also be considered. **If a participant experiences treatment-related Grade 2 or higher CRS, dosing in that participant must be discontinued**.

Grading of Cytokine Release Syndrome

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Cytokine release syndrome	Fever with or without constitutional symptoms	Hypotension responding to fluids; hypoxia responding to $< 40\%$ O_2	Hypotension managed with one pressor; hypoxia requiring $\geq 40\%$ O_2	Life-threatening consequences; urgent intervention indicated

National Cancer Institute Common Terminology Criteria for Adverse Events v5.0

Other Laboratory Abnormalities and Clinical Events

- Grade 3 or 4 clinically significant laboratory abnormalities should be confirmed by repeat testing as soon as possible, and preferably within 3 calendar days after receipt of the original test results. The study drug may be continued without dose interruption for a clinically insignificant Grade 3 and 4 laboratory abnormality (eg, CK elevation after strenuous exercise, triglyceride elevation that is nonfasting or that can be medically managed). Recurrence of laboratory abnormalities considered unrelated to the study drug may not require permanent discontinuation

- Grade 3 or 4 clinical events if considered unrelated to the study drug may not require dose interruption and continuation of the study drug is at the discretion of the investigator

The Gilead medical monitor should be consulted prior to study drug discontinuation when medically feasible.

7.7.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

- Continue study drug at the discretion of the investigator (with the exception of Grade 2 CRS where dosing must be discontinued as detailed in Section 7.7)

7.7.2. Grades 3 Laboratory Abnormality or Clinical Event

- For a Grade 3 clinically significant laboratory abnormality or clinical event, the study drug may be continued if the event is considered to be unrelated to the study drug

- For a Grade 3 clinically significant laboratory abnormality or clinical event confirmed by repeat testing, that is considered to be related to the study drug, then the study drug should be permanently discontinued and the participant managed according to local practice. Recurrence of laboratory abnormalities considered unrelated to the study drug may not require permanent discontinuation

7.7.3. Grades 4 Laboratory Abnormality or Clinical Event

- For a Grade 4 clinical event or clinically significant laboratory abnormality confirmed by repeat testing considered to be related to the study drug, study drug should be permanently discontinued and the participant managed according to local practice. The participant should be followed as clinically indicated until the laboratory abnormality returns to baseline or is otherwise explained, whichever occurs first. A clinically significant Grade 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade

Treatment-emergent toxicities will be noted by the investigator and brought to the attention of the Gilead medical monitor, and the appropriate course of action will be discussed and decided. Whether or not considered treatment related, all participants experiencing AEs must be monitored periodically until symptoms subside, any abnormal laboratory values have resolved or returned to baseline levels or they are considered irreversible, or until there is a satisfactory explanation for the changes observed.

Any questions regarding toxicity management should be directed to the Gilead medical monitor.

8. STATISTICAL CONSIDERATIONS

Details of the statistical methods will be provided in the statistical analysis plan, including any deviations from the original statistical analyses planned.

8.1. Analysis Objectives and Endpoints

Objectives and endpoints are listed in Section 2.

8.2. Planned Analyses

8.2.1. Interim Analysis

Prior to the final analysis, interim analyses may be conducted after each cohort has completed the study.

8.2.2. Final Analysis

The final analysis will be performed after all participants have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

8.3. Analysis Conventions

8.3.1. Analysis Sets

8.3.1.1. All Enrolled Analysis Set

The All Enrolled Analysis Set includes all participants enrolled into the study after screening. This is the primary analysis set for safety listings.

8.3.1.2. Safety Analysis Set

The Safety Analysis Set will include all enrolled participants who received at least 1 dose of study drug. Participants who received treatment other than that to which they were assigned will be analyzed according to the treatment received.

8.3.1.3. Pharmacokinetics Analysis Set

The PK Analysis Set will include all enrolled participants who received at least 1 dose of VES and had at least 1 nonmissing PK concentration datum reported by PK laboratory for each respective analyte.

8.3.1.4. Biomarker Analysis Set

The Biomarker Analysis Set will include all enrolled participants who received at least 1 dose of study drug and have at least 1 blood sample collected for biomarker evaluation after administration of study drug.

8.3.2. Data Handling Conventions

The rule for handling PK concentration values below the limit of quantitation will described in the statistical analysis plan.

Laboratory data that are continuous in nature but are less than the lower limit of quantitation or above the upper limit of quantitation will be imputed to the value of the lower or upper limit minus or plus 1 significant digit, respectively (eg, if the result of a continuous laboratory test is less than 20, a value of 19 will be assigned; if the result of a continuous laboratory test is less than 20.0, a value of 19.9 will be assigned).

Missing data can have an impact upon the interpretation of the study data. As this study is of short duration, it is anticipated that missing data will be minimal. In general, values for missing data will not be imputed. However, a missing pretreatment laboratory result would be treated as normal (ie, no toxicity grade) for the laboratory abnormality summary.

8.4. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized and descriptive statistics will be provided.

Demographic summaries will include sex, race/ethnicity, and age.

Baseline data will include a summary of weight and BMI.

8.5. Safety Analysis

All safety data collected on or after the date that study drug was first administered up to the study completion will be summarized by treatment (according to the study drug received) using the Safety Analysis Set.

8.5.1. Extent of Exposure

A participant's extent of exposure to study drug data will be generated from the study drug administration data. Exposure data will be listed.

8.5.2. Adverse Events

Clinical and laboratory AEs will be coded using the current version of the MedDRA. System organ class (SOC), high-level group term, high-level term, preferred term (PT), and lower-level term will be attached to the clinical database.

Adverse event data will be listed by participant. Treatment-emergent AEs, serious TEAEs, and TEAEs leading to discontinuation of treatment will be summarized by treatment, SOC, and PT using the current version of MedDRA.

8.5.3. Laboratory Evaluations

Listings of individual participant laboratory results will be provided. Laboratory results and changes from predose values for selected laboratory tests will be summarized by cohort at scheduled visits. The incidence of treatment-emergent graded laboratory abnormalities will be summarized by treatment.

8.5.4. Other Safety Evaluations

Vital signs and ECG data will be summarized by cohort over time.

8.6. Pharmacokinetic Analysis

Plasma concentrations and PK parameters will be listed and summarized for each analyte using descriptive statistics by treatment, as applicable.

In addition, for Cohorts 1 and 2, an analysis of variance using a mixed-effects model with treatment as a fixed effect and participant as a random effect will be fitted to the natural logarithmic transformation of PK parameters (AUC_{last}, AUC_{inf}, and C_{max}) for each analyte. Two-sided 90% CIs will be calculated for the ratios of geometric least-squares means (GLSMs) between test and reference treatments being compared.

8.7. Biomarker Analysis

The absolute level of PD biomarkers (including serum cytokines, ISGs mRNA, and immune cell phenotype), their change from baseline, and fold change from baseline will be listed and summarized using descriptive statistics by treatment within each cohort.

The absolute and normalized levels of TruCulture cytokines, as well as their association with serum PD biomarkers will be evaluated.

8.8. Sample Size

With 18 evaluable participants per cohort, the estimated 2-sided 90% CI of the GLSM ratio of test versus reference treatments with regards to AUC_{inf} and C_{max} will be within (0.50, 2.00) with at least 90% probability if the true GLSM ratio was 1.0. This is assuming a root mean square error of no more than 0.6 on a natural logarithm scale, which is supported by the previous Study GS-US-234-0101. With 35% and 10% overage for Cohorts 1 and 2, a total sample size of 25 participants and 20 participants will be required for Cohorts 1 and 2, respectively.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with International Council for Harmonisation (ICH) E6(R2) GCP and applicable laws and regulations.

9.1.2. Financial Disclosure

The investigator and subinvestigators will provide prompt and accurate documentation of their financial interest or arrangements with the sponsor or proprietary interests in the study drug. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last participant completes the protocol-defined activities.

9.1.3. Institutional Review Board Review and Approval

The investigator (or Gilead as appropriate according to local regulations) will submit this protocol, ICF, and any accompanying material to be provided to the participant (such as advertisements, participant information sheets, or descriptions of the study used to obtain informed consent) to an IRB. The investigator will not begin any study participant activities until approval from the IRB has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB for any modifications made to the protocol or any accompanying material to be provided to the participant after initial IRB approval, with the exception of those necessary to reduce immediate risk to study participants.

9.1.4. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study before undertaking any study-related procedures. The investigator must use the most current IRB-approved ICF for documenting written informed consent. Each ICF will be appropriately signed and dated by the participant, the person conducting the consent discussion, and also by an impartial witness if required by the IRB or local requirements.

The ICF will inform participants about genomic testing and/or planned sample retention.[CCI]

[redacted]

CCI [redacted]

9.1.5. Confidentiality

The investigator must ensure that participants' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code and any other unique identifier(s) as allowed by local law (such as year of birth) will be recorded on any form or biological sample submitted to Gilead, IRB, or the laboratory. Laboratory specimens must be labeled in such a way as to protect participant identity while allowing the results to be recorded to the proper participant. Refer to specific laboratory instructions. NOTE: The investigator must keep a screening log with details for all participants screened and enrolled in the study. Participant data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the IB, this protocol, CRFs, study drug information, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the investigational site to any third party or otherwise into the public domain.

9.1.6. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories: (1) investigator's study file and (2) participant clinical source documents.

The investigator's study file will contain the protocol/amendments, CRFs, IRB, and governmental approval with correspondence, ICF, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each participant:

- Participant identification (name, date of birth, gender)
- Documentation that participant meets eligibility criteria, ie, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria)
- Documentation of the reason(s) a consented participant is not enrolled
- Participation in study (including study number)

- Study discussed and date of informed consent
- Dates of all visits
- Documentation that protocol-specific procedures were performed
- Results of efficacy parameters, as required by the protocol
- Start and end dates (including dose regimen) of study drug, including dates of dispensing and return
- Record of all AEs and other safety parameters (start and end date; causality and severity), and documentation that adequate medical care has been provided for any AE
- Concomitant medication (including start and end dates, dose if relevant, and dose changes)
- Date of study completion and reason for early discontinuation, if it occurs

All clinical study documents must be retained by the investigator for at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, US, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, for 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the participant, appropriate copies should be made for storage away from the site.

9.1.7. Case Report Forms

An eCRF casebook will be completed by an authorized study personnel member whose training for this function is completed in the EDC system unless otherwise directed. The eCRF casebook will only capture the data required per the protocol schedule of events and procedures, unless collected by a nonelectronic data capture vendor system (eg, central laboratory). The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only after all data related to eligibility are available. Data entry should be performed in accordance with the CRF Completion Guidelines provided by the sponsor. Subsequent to data entry, a study monitor may perform source data verification. System-generated or manual queries will be issued in the EDC system as data discrepancies are identified by the study monitor or Gilead personnel who routinely review the data for completeness, correctness, and consistency. The site investigator,

site coordinator, or other designee is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. Regular oversight by the PI of the data entered into the EDC system is expected to occur on an ongoing basis throughout the study to ensure quality and completeness. At a minimum, before any interim, final, or other time points (as instructed by Gilead), the investigator will apply his/her electronic signature to confirm that the forms have been reviewed and that the entries accurately reflect the information in the source documents. At the conclusion of the study, Gilead will provide the site investigator with a read-only archive copy of the data entered. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.6.

9.1.8. Investigator Inspections

The investigator will make available all source documents and other records for this study to Gilead's appointed study monitors, to IRB, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study participants, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB in accordance with local requirements and receive documented IRB approval before modifications may be implemented.

9.2.2. Study Reports and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency(ies) when applicable and in accordance with local regulatory requirements. Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases. For studies with sites in countries following the EU Regulation No. 536/2014, a CSR will be submitted within 1 year after the global end of study (as defined in Section 3.5.2).

Investigators in this study may communicate, orally present, or publish study data in scientific journals or other scholarly media in accordance with the Gilead clinical trial agreement.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol (eg, attendance at investigator's meetings). If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to federal and state agencies any expenses paid or reimbursed for such services, including any clinical study payments, meal and/or travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation and any participant records in order to verify the adherence to the protocol and accuracy of the data recorded in the CRFs. The study monitor is responsible for routine review of the CRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The investigator agrees to cooperate with the study monitor to ensure that any problems detected through any type of monitoring (central, off-site, on-site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead study monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Gilead reserves the right to terminate the study at any time, and the investigator has the right to terminate the study at his or her site. Should this be necessary, both parties will arrange discontinuation procedures and notify the participants, appropriate regulatory authority(ies), and IRB. In terminating the study, Gilead and the investigator will ensure that adequate consideration is given to the protection of the participants' interests.

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11. APPENDICES

11.1. Investigator Signature Page

GILEAD SCIENCES, INC.
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FOSTER CITY, CA 94404
USA

STUDY ACKNOWLEDGEMENT

A Phase 1, Open-label, Multicohort Study to Evaluate the Impact of Inhibitors and Inducers of Cytochrome P450 Enzyme (CYP)3A and/or P-glycoprotein (P-gp) on the Pharmacokinetics (PK) of Vesatolimod (VES) in Virologically Suppressed Adults With HIV-1 on Antiretroviral Therapy (ART)

Amendment 3 12 December 2022

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPD

Medical Monitor

[See appended electronic signature]

Signature

[See appended electronic signature]

Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)

Signature

Date

Site Number

11.2. Pandemic Risk Assessment and Mitigation Plan

During an ongoing pandemic, potential risks associated with participants being unable to attend study visits have been identified for this study.

These risks can be summarized as follows:

1) Study drug supplies to participants and sites:

    a) Shipments of study drug could be delayed because of transportation issues. Without study drugs, the participant would not be able to continue receiving the study drug as planned per protocol.

    Mitigation plan: The sites study drug inventory should be closely monitored. Site staff should notify the sponsor or delegate if they foresee shortage in study drug inventory or if there is any interruption in local shipping service. The sponsor will continue to monitor inventory at the study drug depot and investigational sites. Manual shipments will be triggered as necessary.

2) Participant safety monitoring and follow-up:

    a) Participants may be unable or unwilling to come to the investigational site for their scheduled study visits as required per protocol.

    Mitigation plan: For participants who may be unable or unwilling to visit the investigational site for their scheduled study visits as required per protocol, the PI or qualified delegate will conduct a virtual study visit, via phone or video conferencing, to assess the participant within target visit window date whenever possible. During the remote study visit, the following information at minimum will be reviewed:

        i) Confirm if participant has experienced any adverse events (AEs)/serious adverse events (SAEs)/special situations (including pregnancy) and follow-up on any unresolved AE/SAEs.

        ii) Review current list of concomitant medications and document any new concomitant medications.

        iii) If applicable, confirm electronic diary questionnaires and patient-reported outcomes have been completed and transmitted.

        iv) If applicable, confirm participant's study drug supply is sufficient to last until the next planned visit date. If study drug resupply is needed it will be provided as described above in (1).

        v) If applicable, remind participant to maintain current dosing and to keep all dispensed study drug kits for return at the next on-site visit.

b) Participants may be unable or unwilling to travel to the site for planned assessments (eg, safety blood draws); hence samples may not be sent for central laboratory analyses.

Mitigation plan: Local laboratories or other vendors may be utilized as appropriate to monitor participant safety until the participant can return to the site for their regular follow-up visit per protocol. Any changes in the party conducting laboratory assessments for the study due to the pandemic will be documented accordingly. Pregnancy testing may be performed using a home urine pregnancy test if local laboratory pregnancy testing is not feasible.

c) Participants may be unable or unwilling to attend the study visit to sign an updated ICF version.

Mitigation plan: The site staff will follow their approved consent process and remain in compliance with local IRB and national laws and regulations. Remote consent will be allowed if has been approved by the local IRB. The consent process will be documented and confirmed by normal consent procedure at the earliest opportunity.

3) Protocol and monitoring compliance:

d) Protocol deviations may occur in case scheduled visits cannot occur as planned per protocol.

Mitigation plan: If it is not possible to complete a required procedure, an unscheduled visit should be conducted as soon as possible when conditions allow. The situation should be recorded and explained as a protocol deviation. Any missed participant visits or deviation to the protocol due to the pandemic must be reported in the eCRF and described in the clinical study report (CSR). Any virtual study visits that are conducted in lieu of clinic visits due to the pandemic will be documented as a protocol deviation related to the pandemic.

e) Study monitors may be unable to carry out source data review or source data verification (SDV), or study drug accountability or assess protocol and Good Clinical Practice compliance. This may lead to delays in SDV, an increase in protocol deviations, or underreporting of AEs.

Mitigation plan: The study monitor is to remain in close communication with the site to ensure data entry and query resolution. Remote SDV may be arranged if allowed. The study monitor is to reference the Study Monitoring Plan for guidance on how to conduct a remote monitoring visit. The study staff is to save and document all relevant communication in the study files. The status of sites that cannot accept monitoring visits and/or participants on site must be tracked centrally and updated on a regular basis.

4) Missing data and data integrity:

    f) There may be an increased amount of missing data due to participants missing visits/assessments. This could have an impact on the analysis and the interpretation of clinical study data.

        Mitigation plan: Implications of a pandemic on methodological aspects for the study will be thoroughly assessed and documented, and relevant actions will be taken as appropriate (ie, modification of the statistical analysis plan) and in compliance with regulatory authorities' guidance. Overall, the CSR will describe the impact of the pandemic on the interpretability of study data.

Risks will be assessed continuously, and temporary measures will be implemented to mitigate these risks as part of a mitigation plan, as described above. These measures will be communicated to the relevant stakeholders as appropriate and are intended to provide alternate methods that will ensure the evaluation and assessment of the safety of participants who are enrolled in this study.

Since these potential risks are considered mitigated with the implementation of these measures, the expected benefit-risk assessment of VES in study participants will remain unchanged.

11.3. Pregnancy Precautions, Definition of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a participant assigned female at birth is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming postmenopausal unless the participant is permanently sterile or has medically documented ovarian failure.

Participants assigned female at birth are considered to be in a postmenopausal state when they are at least 54 years of age with cessation of previously occurring menses for at least 12 months without an alternative cause. In addition, participants assigned female at birth younger than 54 years with amenorrhea of at least 12 months also may be considered postmenopausal if their follicle-stimulating hormone level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

For the purpose of this study, permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a participant assigned female at birth of any age.

b. Definition of Fertility in a Participant Assigned Male at Birth

For the purposes of this study, a participant assigned male at birth is considered fertile after the initiation of puberty unless the participant is permanently sterile by bilateral orchidectomy or medical documentation.

2) Contraception Requirements for Female Participants Assigned Female at Birth and of Childbearing Potential

a. Study Drug Effects on Pregnancy and Hormonal Contraception

Vesatolimod

The overall potential for genetic toxicity of VES is considered to be low. In developmental toxicity studies in mice and rabbits, dose-developmental findings were observed in the rabbit only at doses that caused maternal toxicity (see VES investigator's brochure [IB], Sections 3.3.5 and 6.1.1.1.2). Such findings included increased incidence of early and late fetal resorptions, reduced fetal weights, and increased incidence of soft tissue/skeletal alterations (malformations and variations) at 15 and 30 mg/kg doses. Given these findings in nonclinical studies, VES has shown the potential for embryofetal developmental effects.

There are no clinical data regarding the use of VES in pregnant women. The effects of VES on an unborn child are unknown. A clinical pharmacokinetic (PK) study evaluating the drug interaction potential of VES has not been conducted; however, based on the non-overlapping metabolic pathways for VES and oral contraceptives, no clinically relevant drug interactions are expected upon coadministration of these agents. Please refer to the latest version of the VES IB for additional information.

Cobicistat

Cobicistat (COBI) use during pregnancy has been evaluated in a limited number of individuals as reported by the Antiretroviral Pregnancy Registry (APR), and available data show no significant difference in the rate of overall birth defects for COBI compared with the background rate for major defects of 2.7% in a United States (US) reference population of the Metropolitan Atlanta Congenital Defects Program. The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in clinically recognized pregnancies in the US general population is 15% to 20%. In animal reproduction studies in rats and rabbits, no evidence of fetal harm was observed with oral administration of COBI during organogenesis at doses that produced exposures up to 1.4 and 3.3 times, respectively, the maximal recommended human dose of 150 mg.

No data are available to make recommendations on the use of COBI with hormonal contraceptives.

Please refer to the latest version of the COBI United States Prescribing Information (USPI) for further human and animal data in pregnancy, and additional information.

Voriconazole

Voriconazole (VOR) can cause fetal harm when administered to a pregnant woman. There are no available data on the use of VOR in pregnant women. In animal reproduction studies, oral VOR was associated with fetal malformations in rats and fetal toxicity in rabbits. Cleft palates and hydronephrosis/hydroureter were observed in rat pups exposed to VOR during organogenesis at and above 10 mg/kg (0.3 times the recommended maintenance dose (RMD) of 200 mg every 12 hours based on body surface area [BSA] comparisons). In rabbits, embryomortality, reduced fetal weight and increased incidence of skeletal variations, cervical ribs, and extrasternal ossification sites were observed in pups when pregnant rabbits were orally dosed at 100 mg/kg (6 times the RMD based on BSA comparisons) during organogenesis. Rats exposed to VOR from implantation to weaning experienced increased gestational length and dystocia, which were associated with increased perinatal pup mortality at the 10 mg/kg dose.

The coadministration of VOR with an oral contraceptive, ethinylestradiol/norethindrone, results in an interaction between these 2 drugs, but is unlikely to reduce the contraceptive effect.

Please refer to the latest version of the VOR USPI for further animal data in pregnancy and additional information.

Rifabutin

There are no adequate and well-controlled studies in pregnant women. Reproduction studies have been carried out in rats and rabbits given rifabutin (RFB) using dose levels up to 200 mg/kg (about 6 to 13 times the recommended human daily dose based on BSA comparisons). No teratogenicity was observed in either species. In rats, given 200 mg/kg/day, (about 6 times the recommended human daily dose based on BSA comparisons), there was a decrease in fetal viability. In rats, at 40 mg/kg/day (approximately equivalent to the recommended human daily dose based on BSA comparisons), RFB caused an increase in fetal skeletal variants. In rabbits, at 80 mg/kg/day (about 5 times the recommended human daily dose based on BSA comparisons), RFB caused maternotoxicity and increase in fetal skeletal anomalies.

Rifabutin may decrease the serum concentration of hormonal contraceptives (ie, ethinylestradiol/norethindrone). Patients should be advised to use additional or alternative methods of contraception.

Please refer to the latest version of the RFB USPI for additional information.

b. Contraception Requirements for Female Participants of Childbearing Potential

The inclusion of participants assigned female at birth and of childbearing potential requires the use of highly effective contraceptive measures with a failure rate of less than 1% per year. They must also not rely on a hormone-containing contraceptive as a form of birth control during the study. They must have a negative serum pregnancy test at screening and a negative pregnancy test at the admission (Day −1) visit before enrollment. Pregnancy tests will be performed at monthly intervals thereafter until the end of contraception requirement.

Duration of required contraception for participants assigned female at birth and of childbearing potential in this clinical study should start from the screening visit until 10 days after the last dose of study drug.

Participants assigned female at birth and of childbearing potential must agree to 1 of the following contraceptive methods:

Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the participant's preferred and usual lifestyle.

Or

Consistent and correct use of 1 of the following methods of birth control listed below:

- Nonhormonal intrauterine device (IUD)
- Bilateral tubal occlusion (upon medical assessment of surgical success)
- Vasectomy in the partner assigned male at birth (upon medical assessment of surgical success)

Inclusion of methods of contraception in this list of permitted methods does not imply that the method is approved in any country or region. Methods should only be used if locally approved.

Participants assigned female at birth and of childbearing potential must also refrain from egg donation and in vitro fertilization from screening through the duration of study treatment and until the end of contraception requirement (ie, 10 days after the last dose of study drug).

3) Contraception Requirements for Participants Assigned Male at Birth

It is theoretically possible that a relevant systemic concentration of study drug may be achieved in a partner assigned female at birth from exposure to the participant's seminal fluid and pose a potential risk to an embryo/fetus. A participant assigned male at birth with a partner assigned female at birth and of childbearing potential must use condoms during treatment and until 10 days after last dose of study drug. If the partner assigned female at birth and of childbearing potential is not pregnant, additional contraception recommendations should also be considered.

Participants assigned male at birth must also refrain from sperm donation/in vitro fertilization during treatment and until the end of contraception requirement.

4) Unacceptable Birth Control Methods

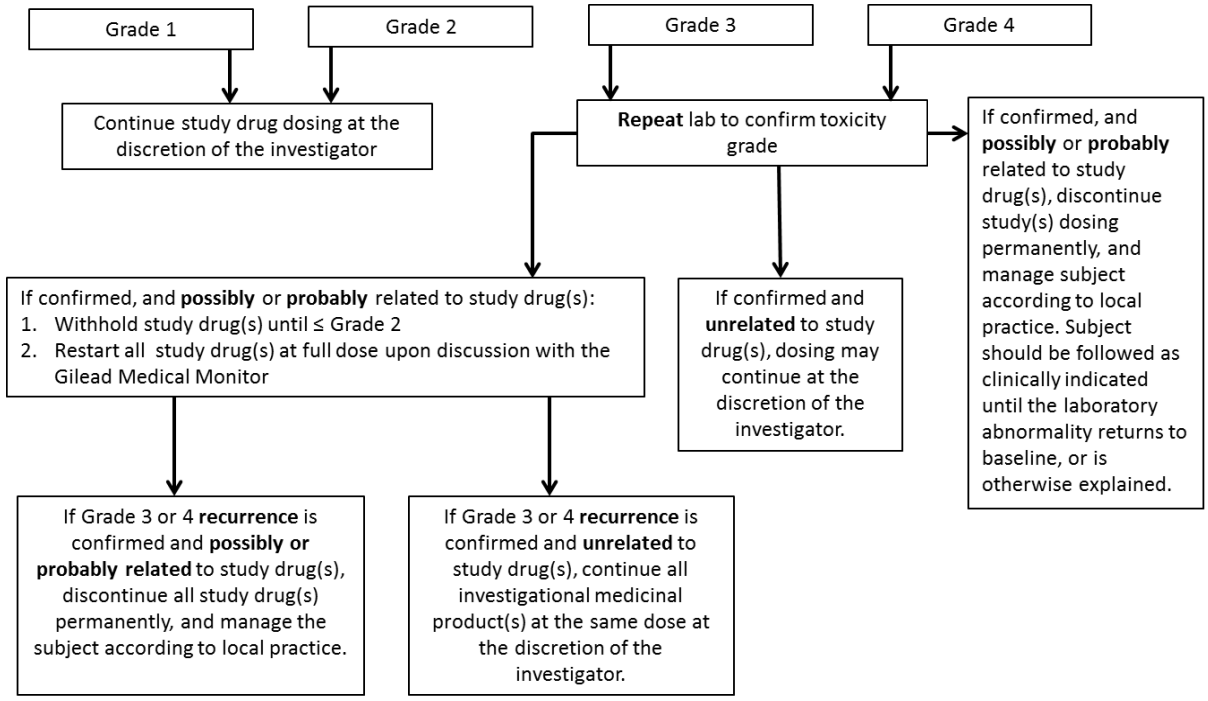
Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal (coitus interruptus), hormone-containing contraceptive only, spermicides only, and lactational amenorrhea method. A female condom and a male condom should not be used together.

5) Procedures to Be Followed in the Event of Pregnancy

Participants assigned female at birth will be instructed to notify the investigator if they become pregnant or suspect they are pregnant at any time during the study, or if they become pregnant within 10 days after the last dose of study drug. Study drug must be discontinued immediately.

Participants assigned male at birth whose partner has become pregnant or suspects they are pregnant from start of study to 10 days after the last study drug dose must also report the information to the investigator. Instructions for reporting pregnancy and pregnancy outcome are outlined in Section 7.4.2.3.

11.4. Management of Clinical and Laboratory Adverse Events



11.5. Gilead Toxicity Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

Antiviral Toxicity Grading Scale, Version 01 April 2015

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin HIV POSITIVE **Adult and Pediatric ≥ 57 Days**	8.5 to 10.0 g/dL 85 to 100 g/L	7.5 to < 8.5 g/dL 75 to < 85 g/L	6.5 to < 7.5 g/dL 65 to < 75 g/L	< 6.5 g/dL < 65 g/L
HIV NEGATIVE **Adult and Pediatric ≥ 57 days**	10.0 to 10.9 g/dL 100 to 109 g/L OR Any decrease from baseline 2.5 to < 3.5 g/dL 25 to < 35 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L OR Any decrease from baseline 3.5 to < 4.5 g/dL 35 to < 45 g/L	7.0 to < 9.0 g/dL 70 to < 90 g/L OR Any decrease from baseline ≥ 4.5 g/dL ≥ 45 g/L	< 7.0 g/dL < 70 g/L
Infant, 36–56 Days (HIV POSITIVE OR NEGATIVE)	8.5 to 9.4 g/dL 85 to 94 g/L	7.0 to < 8.5 g/dL 70 to < 85 g/L	6.0 to < 7.0 g/dL 60 to < 70 g/L	< 6.0 g/dL < 60 g/L
Infant, 22–35 Days (HIV POSITIVE OR NEGATIVE)	9.5 to 10.5 g/dL 95 to 105 g/L	8.0 to < 9.5 g/dL 80 to < 95 g/L	7.0 to < 8.0 g/dL 70 to < 80 g/L	< 7.0 g/dL < 70 g/L
Infant, 1–21 Days (HIV POSITIVE OR NEGATIVE)	12.0 to 13.0 g/dL 120 to 130 g/L	10.0 to < 12.0 g/dL 100 to < 120 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L	< 9.0 g/dL < 90 g/L
Absolute Neutrophil Count **Adult and Pediatric, ≥ 7 Months**[a]	1.00 to 1.30 × 10^9/L 1.00 to 1.30 GI/L	0.75 to < 1.00 × 10^9/L 0.75 to < 1.00 GI/L	0.50 to < 0.75 × 10^9/L 0.50 to < 0.75 GI/L	< 0.50 × 10^9/L < 0.50 GI/L
Absolute CD4 Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	300 to 400/mm^3 300 to 400/µL	200 to < 300/mm^3 200 to < 300/µL	100 to < 200/mm^3 100 to < 200/µL	< 100/mm^3 < 100/µL

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Absolute Lymphocyte Count HIV NEGATIVE ONLY **Adult and Pediatric > 13 Years**	600 to 650/mm^3 0.60 to 0.65 GI/L	500 to < 600/mm^3 0.50 to < 0.60 GI/L	350 to < 500/mm^3 0.35 to < 0.50 GI/L	< 350/mm^3 < 0.35 GI/L
Platelets	100 to < 125 × 10^9/L 100 to < 125 GI/L	50 to < 100 × 10^9/L 50 to < 100 GI/L	25 to < 50 × 10^9/L 25 to < 50 GI/L	< 25 × 10^9/L < 25 GI/L
White Blood Cells	2000/mm^3 to 2500/mm^3 2.00 GI/L to 2.50 GI/L	1500 to < 2000/mm^3 1.50 to < 2.00 GI/L	1000 to < 1500/mm^3 1.00 to < 1.50 GI/L	< 1000/mm^3 < 1.00 GI/L
Hypofibrinogenemia	100 to 200 mg/dL 1.00 to 2.00 g/L	75 to < 100 mg/dL 0.75 to < 1.00 g/L	50 to < 75 mg/dL 0.50 to < 0.75 g/L	< 50 mg/dL < 0.50 g/L
Hyperfibrinogenemia	> ULN to 600 mg/dL > ULN to 6.0 g/L	> 600 mg/dL > 6.0 g/L	— —	— —
Fibrin Split Product	20 to 40 µg/mL 20 to 40 mg/L	> 40 to 50 µg/mL > 40 to 50 mg/L	> 50 to 60 µg/mL > 50 to 60 mg/L	> 60 µg/mL > 60 mg/L
Prothrombin Time	> 1.00 to 1.25 × ULN	> 1.25 to 1.50 × ULN	> 1.50 to 3.00 × ULN	> 3.00 × ULN
International Normalized Ratio of Prothrombin Time	1.1 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 3.0 × ULN	> 3.0 × ULN
Activated Partial Thromboplastin Time	> 1.00 to 1.66 × ULN	> 1.66 to 2.33 × ULN	> 2.33 to 3.00 × ULN	> 3.00 × ULN
Methemoglobin	5.0% to 10.0%	> 10.0% to 15.0%	> 15.0% to 20.0%	> 20.0%

ULN = upper limit of normal

a An overlap between the Grade 1 scale and the laboratory's normal range for absolute neutrophils may result for pediatric participants. Please follow the Gilead convention of grading any result within the lower limit of normal and ULN.

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130 to < LLN mEq/L 130 to < LLN mmol/L	125 to < 130 mEq/L 125 to < 130 mmol/L	121 to < 125 mEq/L 121 to < 125 mmol/L	< 121 mEq/L < 121 mmol/L
Hypernatremia	> ULN to 150 mEq/L > ULN to 150 mmol/L	> 150 to 154 mEq/L > 150 to 154 mmol/L	> 154 to 159 mEq/L > 154 to 159 mmol/L	> 159 mEq/L > 159 mmol/L
Hypokalemia **Adult and Pediatric ≥ 1 Year**	3.0 to < LLN mEq/L 3.0 to < LLN mmol/L	2.5 to < 3.0 mEq/L 2.5 to < 3.0 mmol/L	2.0 to < 2.5 mEq/L 2.0 to < 2.5 mmol/L	< 2.0 mEq/L < 2.0 mmol/L
Infant < 1 Year	3.0 to 3.4 mEq/L 3.0 to 3.4 mmol/L	2.5 to < 3.0 mEq/L 2.5 to < 3.0 mmol/L	2.0 to < 2.5 mEq/L 2.0 to < 2.5 mmol/L	< 2.0 mEq/L < 2.0 mmol/L
Hyperkalemia **Adult and Pediatric ≥ 1 Year**	5.6 to 6.0 mEq/L 5.6 to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
Infant < 1 Year	> ULN to 6.0 mEq/L > ULN to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
Hypoglycemia **Adult and Pediatric ≥ 1 Month**	55 to 64 mg/dL 3.03 to 3.58 mmol/L	40 to < 55 mg/dL 2.20 to < 3.03 mmol/L	30 to < 40 mg/dL 1.64 to < 2.20 mmol/L	< 30 mg/dL < 1.64 mmol/L
Infant < 1 Month	50 to 54 mg/dL 2.8 to 3.0 mmol/L	40 to < 50 mg/dL 2.2 to < 2.8 mmol/L	30 to < 40 mg/dL 1.7 to < 2.2 mmol/L	< 30 mg/dL < 1.7 mmol/L
Hyperglycemia (nonfasting)	116 to 160 mg/dL 6.42 to 8.91 mmol/L	> 160 to 250 mg/dL > 8.91 to 13.90 mmol/L	> 250 to 500 mg/dL > 13.90 to 27.79 mmol/L	> 500 mg/dL > 27.79 mmol/L
Hyperglycemia (fasting)	110 to 125 mg/dL 6.08 to 6.96 mmol/L	> 125 to 250 mg/dL > 6.96 to 13.90 mmol/L	> 250 to 500 mg/dL > 13.90 to 27.79 mmol/L	> 500 mg/dL > 27.79 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypocalcemia (corrected for albumin if appropriate[a]) **Adult and Pediatric ≥ 2 Years**	7.8 to < LLN mg/dL 1.94 to < LLN mmol/L	7.0 to < 7.8 mg/dL 1.74 to < 1.94 mmol/L	6.1 to < 7.0 mg/dL 1.51 to < 1.74 mmol/L	< 6.1 mg/dL < 1.51 mmol/L
Pediatric ≥ 7 Days to 2 Years	7.8 to 8.4 mg/dL 1.94 to 2.10 mmol/L	7.0 to < 7.8 mg/dL 1.74 to < 1.94 mmol/L	6.1 to < 7.0 mg/dL 1.51 to < 1.74 mmol/L	< 6.1 mg/dL < 1.51 mmol/L
Infant < 7 Days	6.5 to 7.5 mg/dL 1.61 to 1.88 mmol/L	6.0 to < 6.5 mg/dL 1.49 to < 1.61 mmol/L	5.5 to < 6.0 mg/dL 1.36 to < 1.49 mmol/L	< 5.5 mg/dL < 1.36 mmol/L
Hypercalcemia (corrected for albumin if appropriate[a]) **Adult and Pediatric ≥ 7 Days**	> ULN to 11.5 mg/dL > ULN to 2.88 mmol/L	> 11.5 to 12.5 mg/dL > 2.88 to 3.13 mmol/L	> 12.5 to 13.5 mg/dL > 3.13 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Infant < 7 Days	11.5 to 12.4 mg/dL 2.86 to 3.10 mmol/L	> 12.4 to 12.9 mg/dL > 3.10 to 3.23 mmol/L	> 12.9 to 13.5 mg/dL > 3.23 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L
Hypocalcemia (ionized)	3.0 mg/dL to <LLN 0.74 mmol/L to <LLN	2.5 to < 3.0 mg/dL 0.62 to < 0.74 mmol/L	2.0 to < 2.5 mg/dL 0.49 to < 0.62 mmol/L	< 2.0 mg/dL < 0.49 mmol/L
Hypercalcemia (ionized)	>ULN to 6.0 mg/dL >ULN to 1.50 mmol/L	> 6.0 to 6.5 mg/dL > 1.50 to 1.63 mmol/L	> 6.5 to 7.0 mg/dL > 1.63 to 1.75 mmol/L	> 7.0 mg/dL > 1.75 mmol/L
Hypomagnesemia	1.40 to < LLN mg/dL 1.2 to < LLN mEq/L 0.58 to < LLN mmol/L	1.04 to < 1.40 mg/dL 0.9 to < 1.2 mEq/L 0.43 to < 0.58 mmol/L	0.67 to < 1.04 mg/dL 0.6 to < 0.9 mEq/L 0.28 to < 0.43 mmol/L	< 0.67 mg/dL < 0.6 mEq/L < 0.28 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypophosphatemia **Adult and Pediatric > 14 Years**	2.0 to < LLN mg/dL 0.63 to <LLN mmol/L	1.5 to < 2.0 mg/dL 0.47 to < 0.63 mmol/L	1.0 to < 1.5 mg/dL 0.31 to < 0.47 mmol/L	< 1.0 mg/dL < 0.31 mmol/L
Pediatric 1–14 Years	3.0 to < LLN mg/dL 0.96 to < LLN mmol/L	2.5 to < 3.0 mg/dL 0.80 to < 0.96 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Pediatric < 1 Year	3.5 to < LLN mg/dL 1.12 to < LLN mmol/L	2.5 to < 3.5 mg/dL 0.80 to < 1.12 mmol/L	1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.5 mg/dL < 0.47 mmol/L
Hyperbilirubinemia **Adult and Pediatric > 14 Days**	> 1.0 to 1.5 × ULN	> 1.5 to 2.5 × ULN	> 2.5 to 5.0 × ULN	> 5.0 × ULN
Infant ≤ 14 Days (nonhemolytic)	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 to 30.0 mg/dL > 428 to 513 µmol/L	> 30.0 mg/dL > 513 µmol/L
Infant ≤ 14 Days (hemolytic)	NA	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 mg/dL > 428 µmol/L
Blood Urea Nitrogen	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Hyperuricemia	> ULN to 10.0 mg/dL > ULN to 597 µmol/L	> 10.0 to 12.0 mg/dL > 597 to 716 µmol/L	> 12.0 to 15.0 mg/dL > 716 to 895 µmol/L	> 15.0 mg/dL > 895 µmol/L
Hypouricemia **Adult and Pediatric ≥ 1 Year**	1.5 mg/dL to <LLN 87 µmol/L to <LLN	to < 1.5 mg/dL 57 to < 87 µmol/L	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L
Infant < 1 Year	N/A	mg/dL to < LLN 57 µmol/L to < LLN	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L
Creatinine[b]	> 1.50 to 2.00 mg/dL > 133 to 177 µmol/L	> 2.00 to 3.00 mg/dL > 177 to 265 µmol/L	> 3.00 to 6.00 mg/dL > 265 to 530 µmol/L	> 6.00 mg/dL > 530 µmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Bicarbonate **Adult and Pediatric ≥ 4 Years**	16.0 mEq/L to < LLN 16.0 mmol/L to < LLN	11.0 to < 16.0 mEq/L 11.0 to < 16.0 mmol/L	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L
Pediatric < 4 Years	NA	11.0 mEq/L to < LLN 11.0 mmol/L to < LLN	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L
Triglycerides (fasting)	NA	500 to 750 mg/dL 5.64–8.47 mmol/L	> 750 to 1200 mg/dL > 8.47 to 13.55 mmol/L	> 1200 mg/dL > 13.55 mmol/L
Low-Density Lipoprotein (fasting) **Adult**	130 to 160 mg/dL 3.35 to 4.15 mmol/L	> 160 to 190 mg/dL > 4.15 to 4.92 mmol/L	> 190 mg/dL > 4.92 mmol/L	NA
Low-Density Lipoprotein (fasting) **Pediatric > 2 to < 18 Years**	110 to 130 mg/dL 2.84 to 3.37 mmol/L	> 130 to 190 mg/dL > 3.37 to 4.92 mmol/L	> 190 mg/dL > 4.92 mmol/L	NA
Hypercholesterolemia (fasting)	200 to 239 mg/dL 5.16 to 6.19 mmol/L	> 239 to 300 mg/dL > 6.19 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
Pediatric < 18 Years	170 to 199 mg/dL 4.39 to 5.15 mmol/L	> 199 to 300 mg/dL > 5.15 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
Creatine Kinase	3.0 to < 6.0 × ULN	6.0 to < 10.0 × ULN	10.0 to < 20.0 × ULN	≥ 20.0 × ULN

LLN = lower limit of normal; ULN = upper limit of normal

a Calcium should be corrected for albumin if albumin is < 4.0 g/dL

b An overlap between the Grade 1 scale and the laboratory's normal range for creatinine may result for male participants > 70 years. Please follow the Gilead convention of grading any result within the lower limit of normal (LLN) and upper limit of normal (ULN).

ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT)	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
ALT (SGPT)	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
GGT	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Alkaline Phosphatase	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Total Amylase	> 1.0 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 5.0 × ULN	> 5.0 × ULN
Pancreatic Amylase	> 1.0 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 5.0 × ULN	> 5.0 × ULN
Lipase	> 1.0 to 1.5 × ULN	> 1.5 to 3.0 × ULN	> 3.0 to 5.0 × ULN	> 5.0 × ULN
Albumin **Pediatric < 16 Years** **Adult and Pediatric ≥ 16 Years**	- 3.0 g/dL to <LLN 30 g/L to <LLN	2.0 g/dL to <LLN 20 g/L to <LLN 2.0 to < 3.0 g/dL 20 to < 30 g/L	< 2.0 g/dL < 20 g/L < 2.0 g/dL < 20 g/L	NA NA

ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; LLN = lower limit of normal; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; ULN = upper limit of normal

URINALYSIS				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hematuria (dipstick)	1+	2+	3-4+	NA
Hematuria (quantitative) See Note below				
Females	> ULN to 10 RBC/HPF	> 10 to 75 RBC/HPF	> 75 RBC/HPF	NA
Males	6 to 10 RBC/HPF	> 10 to 75 RBC/HPF	> 75 RBC/HPF	NA
Proteinuria (dipstick)	1+	2–3+	4+	NA
Proteinuria, 24-Hour Collection				
Adult and Pediatric ≥ 10 Years	200 to 999 mg/24 h	> 999 to 1999 mg/24 h	> 1999 to 3500 mg/24 h	> 3500 mg/24 h
Pediatric > 3 Months to < 10 Years	201 to 499 mg/m^2/24 h	> 499 to 799 mg/m^2/24 h	> 799 to 1000 mg/m^2/24 h	> 1000 mg/m^2/24 h
Glycosuria (dipstick)	1+	2-3+	4+	NA

RBC/HPF = red blood cells per high power field
Notes:

- Toxicity grades for quantitative and dipstick hematuria will be assigned by Covance laboratory; however, for other laboratories, toxicity grades will only be assigned to dipstick hematuria.
- With the exception of lipid tests, any graded laboratory test with a result that is between the lower limit of normal and upper limit of normal should be assigned Grade 0.
- If the severity of a clinical adverse event (AE) could fall under either 1 of 2 grades (eg, the severity of an AE could be either Grade 2 or Grade 3), select the higher of the 2 grades for the AE.

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cardiac Arrhythmia (general) (by ECG or physical examination)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/Infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs indicated (for children ≤ 10 cc/kg) indicated
Hypertension (with repeat testing at same visit)	140 to 159 mm Hg systolic OR 90 to 99 mm Hg diastolic	> 159 to 179 mm Hg systolic OR > 99 to 109 mm Hg diastolic	> 179 mm Hg systolic OR > 109 mm Hg diastolic	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization (other than ER visit) indicated
Pediatric ≤ 17 Years (with repeat testing at same visit)	NA	91st to 94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Pericardial Effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life-threatening physiologic consequences OR Effusion with nonurgent intervention indicated	Life-threatening consequences (eg, tamponade) OR Urgent intervention indicated
Prolonged PR Interval	PR interval 0.21 to 0.25 sec	PR interval > 0.25 sec	Type II second degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
Pediatric ≤ 16 Years	1st degree AV block (PR > normal for age and rate)	Type I second degree AV block	Type II second degree AV block	Complete AV block
Prolonged QTc	Asymptomatic, QTc interval 0.45 to 0.47 sec OR Increase interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 to 0.49 sec OR Increase in interval 0.03 to 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia
Pediatric ≤ 16 Years	Asymptomatic, QTc interval 0.450 to 0.464 sec	Asymptomatic, QTc interval 0.465 to 0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/Embolism	NA	Deep vein thrombosis AND No intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Embolic event (eg, pulmonary embolism, life-threatening thrombus)
Vasovagal Episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular Dysfunction (congestive heart failure [CHF])	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic CHF	Life-threatening CHF

AV = atrioventricular; ECG = electrocardiogram; ER = emergency room; IV = intravenous; RBC = red blood cell

RESPIRATORY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Bronchospasm (acute)	FEV_1 or peak flow reduced to 70% to 80%	FEV_1 or peak flow 50% to 69%	FEV_1 or peak flow 25% to 49%	Cyanosis OR FEV_1 or peak flow < 25% OR Intubation
Dyspnea or Respiratory Distress	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated
Pediatric < 14 Years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90% to 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated

FEV_1 = forced expiratory volume in the first second of expiration

OCULAR/VISUAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual Changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

SKIN				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alopecia	Thinning detectable by study participant or caregiver (for disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous Reaction – Rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving 2 or more distinct mucosal sites OR Toxic epidermal necrolysis
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [eg, tube feeding or total parenteral nutrition]
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (eg, diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (eg, sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (eg, obstruction)
Diarrhea **Adult and Pediatric ≥ 1 Year**	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline/24 hours	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24 hours	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (eg, hypotensive shock)
Pediatric < 1 Year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Mucositis/Stomatitis (clinical examination) See also Proctitis, Dysphagia-Odynophagia	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (eg, aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24-48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than ER visit)	Symptomatic AND Hospitalization indicated (other than ER visit)	Life-threatening consequences (eg, sepsis, circulatory failure, hemorrhage)
Proctitis (functional- symptomatic) Also see Mucositis/Stomatitis for Clinical Exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social/functional activities OR Operative intervention indicated	Life-threatening consequences (eg, perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated	Life-threatening consequences (eg, hypotensive shock)

ER = emergency room; IV = intravenous

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alteration in Personality-Behavior or in Mood (eg, agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (eg, suicidal/homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and Behavioral/Attentional Disturbance (including dementia and Attention Deficit Disorder)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions
Cognitive and Behavioral/Attentional Disturbance (including dementia and Attention Deficit Disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
Central Nervous System Ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (stroke) with neurological deficit
Developmental delay **Pediatric ≤ 16 Years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than ER visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social/functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular Weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizure: (new onset)	NA	1 seizure	2–4 seizures	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)
Seizure: (preexisting) For Worsening of Existing Epilepsy the Grades Should Be Based on an Increase from Previous Level of Control to Any of These Levels	NA	Increased frequency of preexisting seizures (nonrepetitive) without change in seizure character OR infrequent breakthrough seizures while on stable meds in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (eg, severity or focality)	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Seizure **– Pediatric < 18 Years**	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5 to 20 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting > 20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions

ER = emergency room

MUSCULOSKELETAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss **Pediatric < 21 Years**	BMD t-score or z-score –2.5 to –1.0 BMD z-score –2.5 to –1.0	BMD t-score or z-score < –2.5 BMD z-score < –2.5	Pathological fracture (including loss of vertebral height) Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences Pathologic fracture causing life-threatening consequences
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions

BMD = bone mineral density

SYSTEMIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Acute Systemic Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7 °C to 38.6 °C 99.8 °F to 101.5 °F	38.7 °C to 39.3 °C 101.6 °F to 102.8 °F	39.4 °C to 40.5 °C 102.9 °F to 104.9 °F	> 40.5 °C > 104.9 °F
Pain- Indicate Body Site See also Injection Site Pain, Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than ER visit) indicated
Unintentional Weight Loss	NA	5% to 9% loss in body weight from baseline	10% to 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated (eg, tube feeding or total parenteral nutrition)

ER = emergency room

INJECTION SITE REACTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Injection Site Pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than ER visit) indicated for management of pain/tenderness
Injection Site Reaction (localized) **Adult and Pediatric > 15 Years**	Erythema OR Induration of 5 × 5 cm to 9 × 9 cm (or 25-81 cm^2)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pediatric ≤ 15 Years	Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (eg, upper arm/thigh)	Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (eg, upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pruritis Associated with Injection See also Skin: Pruritis (itching—no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 h treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 h treatment	Generalized itching causing inability to perform usual social & functional activities	NA

ER = emergency room

ENDOCRINE/METABOLIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Lipodystrophy (eg, back of neck, breasts, abdomen)	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes Mellitus	NA	New onset without need to initiate medication OR Modification of current meds to regain glucose control	New onset with initiation of indicated med OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (eg, ketoacidosis, hyperosmolar non-ketotic coma)
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, myxedema coma)
Lipoatrophy (eg, fat loss from the face, extremities, buttocks)	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

GENITOURINARY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Intermenstrual Bleeding	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic exam	Intermenstrual bleeding not greater in duration or amount than usual menstrual cycle	Intermenstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary Tract obstruction (eg, stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

INFECTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Infection (any other than HIV infection)	Localized, no systemic antimicrobial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (eg, septic shock)

Basic Self-care Functions: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.
Usual Social & Functional Activities: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

protocol GS-US-382-1587 amd-3

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Research eSigned	PPD