CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2 Study to Evaluate the Efficacy of GS-9131 Functional Monotherapy in HIV-1-Infected Adults Failing a Nucleos(t)ide Reverse Transcriptase Inhibitor-Containing Regimen with Nucleos(t)ide Reverse Transcriptase Inhibitor Resistant Virus	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404	
IND Number:	132376	
EudraCT Number:	Not Applicable	
Clinical Trials.gov Identifier:	NCT03472324	
Indication:	HIV-1 infection	
Protocol ID:	GS-US-442-4148	
Gilead Clinical Program Manager:	Name: Telephone: Fax:	PPD PPD PPD
Gilead Medical Monitor:	Name: Telephone: Fax:	PPD PPD PPD
Protocol Version/Date:	Original: Amendment 1: Amendment 2: Amendment 3:	15 June 2017 24 August 2017 12 October 2018 01 November 2018

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

PROTOCOL SYNOPSIS

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

Study Title:	A Phase 2 Study to Evaluate the Efficacy of GS-9131 Functional Monotherapy in HIV-1-Infected Adults Failing a Nucleos(t)ide Reverse Transcriptase Inhibitor-Containing Regimen with Nucleos(t)ide Reverse Transcriptase Inhibitor Resistant Virus
IND Number:	132376
EudraCT Number:	Not Applicable
Clinical Trials.gov Identifier:	NCT03472324
Study Centers Planned:	Uganda, Zimbabwe
Objectives:	The primary objective of this study is as follows: • To evaluate the short-term antiviral potency of GS-9131 functional monotherapy compared to placebo-to-match (PTM) GS-9131, each administered once daily with the existing failing antiretroviral (ARV) regimen, as demonstrated by the proportion of subjects achieving HIV-1 RNA > 0.5 $\log_{10}$ decreases from baseline through up to 14 days of therapy. The secondary objectives of this study are as follows: **Part 1** • To evaluate the efficacy of GS-9131 functional monotherapy as determined by the change from baseline in $\log_{10}$ HIV-1 RNA at Day 11 (Sentinel Cohort 1) or Day 15 (Sentinel Cohort 2 and Randomized Cohort). **Part 2** • To evaluate the safety and efficacy of a regimen containing GS-9131 (60 mg) + bictegravir (BIC) + darunavir (DRV) + ritonavir (RTV) through 24 weeks of treatment in subjects from Sentinel Cohort 1 who switched from a failing regimen. • To evaluate the safety and efficacy of a regimen containing GS-9131 + bictegravir (BIC) + tenofovir alafenamide (TAF) through 24 weeks of treatment in subjects from Sentinel Cohort 2 and Randomized Cohort who switched from a failing regimen.

- To characterize the pharmacokinetics (PK) of GS-9131 in treatment-experienced patients.
- To evaluate the number of subjects with treatment-emergent nucleos(t)ide reverse transcriptase inhibitor (NRTI), protease inhibitor (PI), and integrase strand-transfer inhibitor (INSTI) mutations at the time of virologic failure.

Study Design:

Part 1: GS-9131 Functional Monotherapy

The study will consist of 3 cohorts - Two Sentinel Cohorts and one Randomized Cohort.

The Sentinel Cohort 1 will enroll 10 TE viremic HIV-1 subjects to receive open-label GS-9131 60 mg for 10 days in addition to their current failing ARV regimen.

Sentinel Cohort 2 will enroll up to 10 TE viremic HIV-1 subjects to receive open-label GS-9131 180 mg for 14 days in addition to their current failing ARV regimen.

Sentinel cohort subjects who meet criteria for Part 2, will transition to Part 2 and not participate in the randomized portion of this study.

The Sentinel Cohorts will be followed by a Randomized Cohort that is a double-blind comparison of the addition of GS-9131 (up to 180 mg), or PTM to the current failing ARV regimen in viremic HIV-1 positive adults. Randomization and dosing into the Randomized Cohort will begin after review of the clinical data in the second Sentinel Cohort.

In the Randomized Cohort, up to 48 subjects failing their current ARV regimen will be randomized 1:1:1:1 to GS-9131 (up to three active dose levels, up to 180 mg), or PTM. The GS-9131 dose for Treatment Arms A-C will be determined following review of the safety, activity and available PK data from Sentinel Cohort 2. GS-9131 will be added to their failing regimen for 14 days as follows:

Treatment Arms A-C: GS-9131 once daily + current failing antiretroviral therapy (ART) regimen (n=12 per Treatment Arm)

Treatment Arm D: PTM + current failing ART regimen (n=12)

Randomization will be stratified by HIV-1 RNA level (≤ 100,000 copies/mL and > 100,000 copies/mL) at screening.

Study medication will be administered by directly observed therapy (DOT).

Part 2: GS-9131 + BIC + DRV + RTV or GS-9131 + BIC + TAF Combination Therapy

GS-9131(60 mg) + BIC (30 mg) + DRV(800 mg) + RTV(100 mg) Regimen (Sentinel Cohort 1)

Subjects who successfully complete all study doses in Sentinel Cohort 1 and show a reduction in plasma HIV RNA > 0.5 $\log_{10}$ from their pre-GS-9131 baseline following functional monotherapy will discontinue their current failing regimen and start an optimized regimen consisting of GS-9131 (60 mg) + BIC + DRV + RTV for at least 24 weeks.

GS-9131(up to 180 mg) + BIC (75 mg) + TAF (25 mg) (Sentinel Cohort 2 and Randomized Cohort)

Subjects who successfully complete all study doses in Sentinel Cohort 2 and Randomized Cohort (A-C), and show a reduction in plasma HIV RNA > 0.5 $\log_{10}$ from their pre-GS-9131 baseline during functional monotherapy will discontinue their current failing regimen and start an optimized regimen consisting of GS-9131 + BIC + TAF for at least 24 weeks. All Subjects randomized to the placebo arm (Cohort D) will discontinue their current failing regimen and start a regimen consisting of GS-9131(180 mg) + BIC + TAF for at least 24 weeks.

CCI [redacted]

An Independent Data Monitoring Committee (IDMC) will review the progress, efficacy, and safety data while the study is ongoing. The committee will convene after all subjects in the randomized cohort have completed Part 1 and after approximately 50% of subjects in Part 2 have completed Week 12 of Part 2 of the study.

Number of Subjects Planned:

Approximately 68 female subjects will be enrolled in this study.

Replacement subjects may be enrolled for subjects who do not complete all procedures in the functional monotherapy treatment for reasons other than discontinuation due to treatment related adverse events (AEs).

Target Population:	HIV-1 infected adult females ≥ 18 years of age failing a 2 nucleoside reverse transcriptase inhibitor (NRTI) + non-nucleoside reverse transcriptase inhibitor (NNRTI) containing treatment regimen with plasma HIV-1 RNA level ≥ 500 copies/mL, evidence of K65R or 3 or more thymidine analog mutations (TAMs) or Q151M, and at least one documented primary resistance associated mutation to NNRTIs.
Duration of Treatment:	Part 1 Sentinel Cohort 1: 10 days. Part 1 Sentinel Cohort 2 and Randomized Cohort : 14 days each Part 2: At least 24 weeks
Diagnosis and Main Eligibility Criteria:	HIV-1 infected subjects who meet the following criteria: • Non-pregnant/non-lactating females, ≥ 18 years of age at Screening. Females of childbearing potential (as defined in Appendix 7) must have a negative serum pregnancy test at Screening and Day 1. • Subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception as described in Appendix 7. • Estimated glomerular filtration rate (eGFR) (Cockcroft-Gault equation) ≥ 70 mL/min • Currently taking a failing ARV regimen that contains an NRTI • HIV-1 RNA ≥ 500 copies/mL at Screening • CD4 > 100 cells/μL at Screening • Have a screening genotype showing at least the following resistance mutation profile (a local genotype at the Screening visit is acceptable for enrollment upon review by the Sponsor): — K65R or — at least 3 TAMs; TAMs are defined as: M41L, D67N, K70R, L210W, T215F/Y, or K219Q/E/N/R in reverse transcriptase (RT) or — Q151M — and at least one primary resistance mutation to an NNRTI • No prior or current ARV regimens containing integrase inhibitor (INSTI) or protease inhibitor (PI) • No evidence of chronic viral hepatitis B or C infection. Note: Subjects with positive hepatitis C virus (HCV) antibody and without detectable HCV RNA are permitted to enroll. No evidence of active AIDS-related opportunistic infection, including tuberculosis.

Study Procedures/ Frequency:

At Screening, laboratory analyses (hematology, chemistry, urinalysis, and serum pregnancy test [for females of childbearing potential]), HIV-1 RNA, cluster determinant 4 (CD4) cell count, vital signs, electrocardiogram (ECG), complete physical examination, and eGFR will be performed. HIV-1 protease, and reverse transcriptase genotype/phenotype, and hepatitis B virus (HBV) and HCV serologies will be analyzed.

Part 1:

Sentinel Cohort 1 (GS-9131 60 mg plus Current Failing Regimen)

Following Screening and Day 1 (baseline) visits, subjects will be required to visit the clinic daily on Days 2-11. All study medication will be delivered by DOT on Days 1-10.

Laboratory analyses (hematology, chemistry, and urinalysis) will be performed at Day 1 (baseline), Day 7, and Day 11. A fasting metabolic profile will be performed on Day 1. Urine and serum pregnancy test (females of childbearing potential only) will be done at Screening and Day 1 and a urine pregnancy test on Day 11; positive urine pregnancy test on Day 11 will be confirmed with a serum pregnancy test. CD4 T cell count will be performed at Screening, Day 1 (baseline), and Day 11. A plasma sample for phenotypic and genotypic testing of HIV-1 resistance will be collected at Screening, Day 1, and Day 11. A complete physical examination will be performed at Screening, Day 1 (baseline), and Day 11. Symptom driven physical exam will be performed on Day 2 and Day 7. ECGs will be performed at Screening, Day 1, and Day 11.

On Day 10, all subjects will participate in a PK evaluation.

Samples for HIV-1 RNA will be collected at Screening, Day 1 (baseline), and Days 2, 3, 7, 10, and 11.

Assessments of AEs and concomitant medications will be performed at each visit.

Sentinel Cohort 2 (GS-9131 180 mg plus Current Failing Regimen) and Randomized Cohort (GS-9131 or PTM plus Current Failing Regimen)

Following Screening and Day 1 (baseline) visits, all study medication will be delivered by DOT on Days 1-14.

Laboratory analyses (hematology, chemistry, and urinalysis) will be performed at Days 1 (baseline), 3, 5, 7, 10, 14, and 15. A fasting metabolic profile will be performed on Day 1. Urine and serum

pregnancy test (females of childbearing potential only) will be done at Screening and Day 1 and a urine pregnancy test on Days 10 and 14; positive urine pregnancy test will be confirmed with a serum pregnancy test. CD4 T cell count will be performed at Screening and Days 1 (baseline), 10, 14, and 15. A plasma sample for phenotypic and genotypic testing of HIV-1 resistance will be collected at Screening and Days 1, 10, 14, and 15. A whole blood sample for genotypic testing of HIV-1 resistance will be collected at Day 1. A complete physical examination will be performed at Screening and Days 1 (baseline), and 14. Symptom driven physical exam will be performed on Days 2 and 7. ECGs will be performed at Screening, Day 1and Day 15.

On Day 14, all subjects will participate in a PK evaluation.

Samples for HIV-1 RNA will be collected at Screening and Days 1 (baseline), 3, 7, 10, 14, and 15.

Assessments of AEs and concomitant medications will be performed at each visit.

Part 2:

GS-9131 + BIC + DRV + RTV Regimen (Sentinel Cohort 1)

Subjects in the Sentinel Cohort 1 who had a > 0.5 $\log_{10}$ decline in HIV-1 RNA in Part 1 will discontinue their current failing regimen and begin treatment with GS-9131 + BIC + DRV + RTV once daily for 24 weeks. Subjects who had a ≤ 0.5 $\log_{10}$ decline in HIV-1 RNA are not eligible to continue onto Part 2 and will be discontinued from the study.

At their Day 1 visit for Part 2, AEs, concomitant medications, drug accountability, vital signs, physical examinations, HIV-1 RNA, estimated GFR, hematology, chemistry, CD4 cell count, and urinalysis will be performed.

All subjects will be required to visit the clinic on Day 1, and Weeks 1, 2, 4, 8, 12, 18, and 24. At each visit, AEs, concomitant medications, drug accountability, hematology, chemistry, HIV-1 RNA, CD4 cell count, vital signs, and estimated GFR will be evaluated. A fasting metabolic profile will be performed on Day 1, Week 12 and 24 visits. A complete physical examination will be done at Day 1, Week 12 and 24 visits. A symptom directed physical examination will be done at all other visits. Urinalysis will be performed at Day 1, and Week 4, 12, and 24 visits. Urine pregnancy test (females of childbearing potential only) will be done on Day 1, and Weeks 4, 8, 12, 18, and 24; positive urine pregnancy test will be confirmed with a serum pregnancy test.

CCI [redacted]

CCI [redacted]

GS-9131 + BIC + TAF (Sentinel Cohort 2 and Randomized Cohort)

Subjects in the Sentinel Cohort 2 or Randomized Cohort (A-C) who had a > 0.5 $\log_{10}$ decline in HIV-1 RNA in Part 1 will discontinue their current failing regimen and begin treatment with GS-9131 + BIC + TAF once daily for 24 weeks. Subjects who had a ≤ 0.5 $\log_{10}$ decline in HIV-1 RNA are not eligible to continue onto Part 2 and will be discontinued from the study. Subjects in Randomized Cohort D will begin treatment with GS-9131(180 mg) + BIC (75 mg) + TAF (25 mg) once daily for 24 weeks after successful completion of Part 1.

At their Day 1 visit for Part 2, AEs, concomitant medications, drug accountability, vital signs, physical examinations, HIV-1 RNA, estimated GFR, hematology, chemistry, CD4 cell count, and urinalysis will be performed.

All subjects will be required to visit the clinic on Day 1, and Weeks 1, 2, 4, 8, 12, 18, and 24. At each visit, AEs, concomitant medications, drug accountability, hematology, chemistry, HIV-1 RNA, CD4 cell count, vital signs, and estimated GFR will be evaluated. A fasting metabolic profile will be performed on Day 1, Week 12 and 24 visits. A complete physical examination will be done at Day 1, Week 12 and 24 visits. A symptom directed physical examination will be done at all other visits. Urinalysis will be performed at Day 1, and Week 4, 12, and 24 visits. Urine pregnancy test (females of childbearing potential only) will be done on Day 1, and Weeks 4, 8, 12, 18, and 24; positive urine pregnancy test will be confirmed with a serum pregnancy test.

CCI [redacted]

CCI [redacted]

CCI [redacted]

Protocol-Specific Stopping Rules

By Subject: Study drug dosing for a subject will be discontinued if that subject experiences a Grade 3 or Grade 4 treatment-emergent adverse event (AE) or confirmed laboratory abnormality judged by the study investigator to be possibly related to study drug, or any serious adverse event (SAE) considered to be possibly related to study drug.

By Sentinel Cohort: Study drug dosing for the Sentinel Cohorts will be discontinued if any of the following criteria is met:

- 2 or more subjects experiencing Grade 3 or Grade 4 treatment-emergent AEs judged by the study investigator to be possibly related to study drug, or
- 2 or more subjects experiencing confirmed Grade 3 or Grade 4 laboratory abnormalities, or
- 2 or more subjects experiencing any SAE that is considered to be possibly related to study drug.

For the Randomized Cohort and Part 2: If 2 or more subjects in the Randomized Cohort who are subsequently assigned to treatment cohorts in Part 2 experience a Grade 3 or 4 treatment-emergent AE leading to study drug discontinuation or an SAE judged by the study investigator to be possibly related to study drug, the IDMC will be convened to review all preliminary safety data generated in subjects dosed to date.

Subjects will be followed as clinically indicated until the treatment-emergent AE or laboratory abnormality returns to baseline or is otherwise explained, whichever occurs first. Grade 3 and 4 laboratory abnormalities that are not confirmed by repeat testing will be managed according to the clinic's practice; a decision to reinitiate dosing may be made by Gilead in consultation with the investigator and after a safety review.

Test Product, Dose, and Mode of Administration:	Part 1 Sentinel Cohort 1: GS-9131 (60 mg) Part 1 Sentinel Cohort 2 and Randomized Cohort: GS-9131 (up to 180 mg) and PTM

	Part 2: Sentinel Cohort 1: GS-9131 (60 mg) + BIC (30 mg) + DRV (800 mg) + RTV (100 mg) Sentinel Cohort 2 and Randomized Cohort: GS-9131 (doses up to 180 mg) + BIC (75 mg) + TAF (25 mg)
Reference Therapy, Dose, and Mode of Administration:	Part 1:Current ARVs Part 2: None

Criteria for Evaluation:

Efficacy:

The primary endpoint is:

- The proportion of subjects with plasma HIV-1 RNA decreases from baseline exceeding 0.5 $\log_{10}$ (copies/mL) at Day15 in the Randomized Cohort.

The secondary endpoints are:

- The change from baseline in plasma $\log_{10}$ HIV-1 RNA (copies/mL) at Day 11 for Sentinel Cohort 1 and Day 15 for Sentinel Cohort 2 and the Randomized Cohort in Part 1.
- The proportion of subjects with plasma HIV-1 RNA < 50 copies/mL at Week 24 as defined by the US FDA Snapshot algorithm. The number of subjects with treatment-emergent NRTI, PI, or INSTI mutations at the time of virologic failure.

Safety:

The safety and tolerability of GS-9131 in subjects who failed an NRTI-containing regimen with NRTI-resistant virus through Day 15, assessed by clinical exams, laboratory parameters and AE reporting.

The safety and tolerability of switching to the regimen of GS-9131 + BIC + DRV + RTV or GS-9131 + BIC + TAF in subjects who failed an NRTI-containing regimen with NRTI-resistant virus through Week 24, assessed by clinical exams, laboratory parameters and AE reporting.

Pharmacokinetics:

Sentinel Cohort 1 (60 mg): Intensive plasma and PBMC samples will be collected in all subjects on Day 10. Serial blood samples for plasma and peripheral blood mononuclear cell (PBMC) PK assessments will be collected at the following timepoints:

Plasma collection on Day 10: Predose (< 5 minutes prior to dosing), 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 24 hours post dose.

PBMC collection on Day 10: Predose (< 5 minutes prior to dosing), 1, 2, 6, and 24 hours post dose.

Sentinel Cohort 2 (180 mg) and Randomized Cohort: Intensive plasma and PBMC PK samples will be collected in all subjects on Day 14. Serial blood samples for plasma and peripheral blood mononuclear cell (PBMC) PK assessments will be collected at the following timepoints:

Plasma collection on Day 14: Predose (< 5 minutes prior to dosing), 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 24 hours post dose.

PBMC collection on Day 14: Predose (< 5 minutes prior to dosing), 1, 2, 6, and 24 hours post dose

The PK of GS-9131 and its metabolite, GS-9148, in plasma, will be evaluated. The PK of GS-9148-diphosphate (DP) in PBMCs and the PK of other analytes may be explored.

CCI

CCI [redacted]	[redacted]
Statistical Methods:	For Part 1, the proportion of subjects with plasma HIV-1 RNA decreases from baseline exceeding 0.5 $\log_{10}$ at Day 15 in the Randomized Cohort will be compared between each active GS-9131 treatment group and the placebo group using Fisher's exact test. The change from baseline in plasma $\log_{10}$ HIV-1 RNA (copies/mL) at Day 15 will be summarized by cohort and treatment group. For Part 2, the proportion of subjects with plasma HIV-1 RNA < 50 copies/mL at Week 24 will be summarized by treatment group using the US FDA-defined Snapshot Algorithm and the missing = failure /excluded approaches for imputing missing HIV-1 RNA values. The 95% confidence interval (CI) of the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 24 will be calculated using the Clopper-Pearson Exact method. In addition, the change from Part 2 baseline (i.e., predose of an optimized regimen consisting GS-9131 in Part 2) in $\log_{10}$ HIV-1 RNA and CD4 cell count at Week 24 will be summarized by treatment group using descriptive statistics. The 95% CI will be calculated. Adverse event data including treatment-emergent AEs and SAEs will be summarized by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) by treatment group in each part and cohort. Listings of individual subject vital signs, 12-lead ECG parameters, and laboratory results will be provided. Laboratory results and change from predose/baseline values for selected tests will be summarized at scheduled visits by treatment group in each part and cohort. The incidence of treatment-emergent laboratory abnormalities will be summarized by treatment group in each part and cohort as well.

	For the sample size and power calculation for the Randomized Cohort in Part 1, assuming that 70% of subjects in each GS-9131 treatment group and 8.3% in the placebo group achieve > 0.5 $\log_{10}$ HIV-1 RNA decrease from baseline at Day 15, a sample size of 12 subjects per treatment group (48 in total) provides 85% power to detect the difference in the response rates between at least one GS-9131 treatment group and the placebo group with a Fisher's exact test to be done at a two-sided alpha level of 0.05.

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

° C	degrees Celsius
° F	degrees Fahrenheit
AE	adverse event
AhR	aryl hydrocarbon receptor
AIDS	acquired immune deficiency syndrome
ALT	alanine aminotransferase
ART	antiretroviral therapy
ARV	Antiretroviral
AST	aspartate aminotransferase
AUC	area under the plasma/serum/peripheral blood mononuclear cell concentration versus time curve
BIC, B	Bictegravir
B/F/TAF	bictegravir/emtricitabine/tenofovir alafenamide
BUN	blood urea nitrogen
CBC	complete blood count
CFR	FDA code of federal regulations
CI	confidence interval
CK	creatine kinase
CL_{cr}	creatinine clearance
C_{max}	the maximum observed serum/plasma/peripheral blood mononuclear (PBMC) concentration of drug
CMH	Cochran-Mantel-Haenszel
C_{tau}	the observed drug concentration at the end of the dosing interval
COBI	cobicistat, Tybost®
CPK	creatine phosphokinase
CRO	contract (or clinical) research organization
CSR	clinical study report
CYP	cytochrome P450
DHHS	Department of Health and Human Services
DOT	Directly observed therapy
DNA	deoxyribonucleic acid
DP	Diphosphate
DRV	darunavir, Prezista®
DTG	dolutegravir, Tivicay®
ECG	Electrocardiogram
eCRF	electronic case report form(s)
eGFR	estimated glomerular filtration rate
EVG	elvitegravir, E
E/C/F/TAF	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, Genvoya®

FAS	full analysis set
FDA	(United States) Food and Drug Administration
FDC	fixed dose combination
FSH	follicle stimulating hormone
F/TAF	emtricitabine/tenofovir alafenamide, Descovy®
FTC/TDF	emtricitabine/tenofovir disoproxil fumarate
GCP	Good Clinical Practice (Guidelines)
GD	gestation day
GSI, Gilead	Gilead Sciences, Inc.
HAART	highly active antiretroviral therapy
HBV	hepatitis B virus
HBcAb	hepatitis B core antibody
HBeAB	hepatitis B virus e-antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HDPE	high-density polyethylene
hERG	human Ether-à-go-go-Related Gene
HIV	human immunodeficiency virus
HLGT	high-level group term
HLT	high-level term
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP, study drug	investigational medicinal products
INSTI	integrase strand-transfer inhibitor
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
IWRS	interactive web response system
KS	Kaposi's sarcoma
LAM	lactational amenorrhea method
LDL	low density lipoprotein
LLT	lower level term
LSM	least-squares mean
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
Min	Inute
mtDNA	mitochondrial DNA

NNRTI	non-nucleoside reverse transcriptase inhibitor
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
N(t)RTI	nucleos(t)ide reverse transcriptase inhibitor
PAH	pulmonary arterial hypertension
PBMC	peripheral blood mononuclear cell
PI	protease inhibitor
PK	Pharmacokinetic
PP	per-protocol
PT	preferred term
PTM	placebo-to-match
PVE	Pharmacovigilance & Epidemiology
PXR	pregnane X receptor
QD	once daily
RNA	ribonucleic acid
RT	reverse transcriptase
RTV	ritonavir, Norvir®
SADR	serious adverse drug reaction
SAE	serious adverse event
SOC	system organ class
SOP	standard operating procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAF	tenofovir alafenamide
TAM	thymidine analogue mutations
TDF	tenofovir disoproxil fumarate, Viread®
TE	treatment experienced
TFV	Tenofovir
UGT1A1	uridine 5'-diphospho-glucuronosyltransferase
ULN	upper limit of the normal range
US	United States
USPI	United States prescribing information
WHO	World Health Organization

1. INTRODUCTION

1.1. Background

Human immunodeficiency virus type 1 (HIV-1) infection is a life-threatening and serious disease of major public health significance, with approximately 37 million people infected worldwide {UNAIDS 2016}. Standard-of-care for the treatment of HIV-1 infection involves the use of a combination of antiretroviral (ARV) drugs to suppress viral replication to below detectable limits, increase cluster determinant 4 (CD4) cell counts, and delay disease progression. While combination ARV therapy for the treatment of HIV-1 infection has been largely successful in reducing the morbidity and mortality associated with HIV disease, there remains a significant medical need for new well-tolerated therapies that take into consideration HIV genetic variability, ARV resistance, and new options for regimen simplification.

A significant proportion of treatment-experienced (TE) HIV-1 infected patients eventually lose virologic, immunologic, or clinical benefit from their current regimens. Highly TE HIV-1-infected patients with resistance to multiple ARV drug classes have very few or no treatment options. These patient populations include: 1) individuals requiring an extensive number of active ARV agents to construct a fully suppressive or partially active regimen; and 2) individuals with extensive nucleoside reverse transcriptase inhibitor (NRTI) resistance in resource limited regions. Tenofovir (TFV)-based ARV regimens are the first-line treatments in the current antiretroviral therapy (ART) global scale-up campaign {World Health Organization (WHO) 2016}; often TFV resistance develops in parallel with resistance to the other ARVs in the regimen, compromising the effectiveness of the regimen. The reported level of TFV resistance ranges from 20% in Europe to more than 50% in sub-Saharan Africa {TenoRes Study Group 2016}.

Developing safe and effective therapies for TE subjects with ARV drug resistance remains a priority. Patients with multiple prior regimen failures and significant drug resistance have limited treatment options {Department of Health and Human Services (DHHS) 2013, Lundgren 2013, Thompson 2010, Williams 2014}. For these individuals, newer treatments are needed to control viral replication, preserve the immune function, and prevent clinical progression. In all patients, the ideal goal of therapy remains complete and durable viral suppression.

1.2. GS-9131

1.2.1. General Information

GS-9131 is the prodrug of a novel adenine nucleotide analog designated GS-9148. GS-9131 displays a favorable in vitro resistance profile that is distinct from current NRTIs. Important advantages of GS-9131 over currently approved nucleos(t)ide reverse transcriptase inhibitors (N[t]RTIs) based on in vitro and nonclinical in vivo studies include the following:

- An in vitro resistance profile that is more favorable compared with approved N(t)RTIs; GS-9131 maintains its in vitro antiretroviral activity against HIV-1 strains with major

N(t)RTI resistance mutations such as M184V, K65R, L74V, and multiple thymidine analog mutations (TAMs); in addition, GS-9131 selects for rare mutations in reverse transcriptase (RT) in vitro (a combination of K70E+D123N+T165I or Q151L), and the selected viruses remain sensitive to many of the currently marketed N(t)RTIs

- A low potential for nephrotoxicity based on the lack of renal toxicities in animal studies, and reduced accumulation in human renal tissue in vitro due to the weak interaction of GS-9131 with the renal organic anion transporters relative to that of other nucleotide analogs
- A low potential to induce mitochondrial-dependent toxicities based on the lack of depletion of mitochondrial DNA (mtDNA) in cells exposed to GS-9131 or GS-9148, which is consistent with the observed weak inhibition of mtDNA polymerase γ by GS-9148-diphosphate (DP)
- Long intracellular half-life of GS-9148-diphosphate (DP) in target cells (> 24 hours) that supports once daily dosing of GS-9131

For further information on GS-9131, refer to the Investigator's Brochure (IB).

1.2.2. Nonclinical Pharmacology and Toxicology

A core battery of safety pharmacology studies have been conducted with GS-9131. (CNS, cardiovascular, respiratory), repeat-dose toxicity, genetic toxicology, reproductive and developmental toxicity, and immunotoxicity studies. GS-9131 is not genotoxic and did not have adverse effects on the CNS, respiratory, or cardiovascular systems.

The NOAELs and estimated margins of exposure for GS-9131 and GS-9148 in female animals, based on the projected steady state clinical exposures in HIV-1 subjects with the 180 mg GS-9131 dose, are presented in Table 1. As GS-9131 is unstable in mouse and rat plasma due to the high esterase levels, prodrug exposure margins in rodents are generally low and could not be calculated in all instances. The predominant circulating metabolite GS-9148 was monitored in all studies and exposure margins are provided in Table 1.

Table 1. Estimated Exposure Margins for GS-9131 and GS-9148 in Female Animals Relative to 180 mg GS-9131

Study Type	Species/ Duration	NOEL/NOAEL (mg/kg/day)[1]	Analyte	AUC_{0-24} (ng•h/mL)	Exposure Margin vs. 180 mg[2]
Repeat Dose	Mouse / 13 weeks	30	GS-9148	5418	1.9
Repeat Dose	Rat / 4 weeks	300	GS-9148	40544	14.2
Repeat Dose	Rat / 26 weeks	100	GS-9148	26,259	9.2
Repeat Dose	Dog / 4 weeks	10	GS-9131	1434	0.8
			GS-9148	6709	2.3
Repeat Dose	Monkey / 39 weeks	30	GS-9131	959	0.5
			GS-9148	4522	1.6
Fertility	Rat / 3 weeks	100	GS-9148	15,157	5.3
Embryo-fetal development	Rat / GD 6-17	300	GS-9148	57919	20.2
	Rabbit / GD 7-17	20	GS-9131	1334	0.7
			GS-9148	5544	1.9
Immunotoxicity (M/F)	Rat / 4 weeks	300	GS-9148	53672	18.7

NOEL = no observed effect level; NOAEL = no observed adverse effect level; ND = not determined; GD = gestation day

1 Female animals, only

2 Based on projected AUC_{tau} exposures of 180 mg GS-9131 (1797 ng•h/mL) and AUC_{tau} exposures of GS-9148 (2865 ng•h/mL) after administration of 60 mg GS-9131 in Sentinel Cohort 1 of Study GS-US-180-4148, assuming dose-linearity

Effects on lymphoid tissues were noted in rats and dogs. In both species, females were generally less sensitive than males. In a 4-week dog study, lymphoid depletion in the thymus was observed at ≥ 3 mg/kg/day in males and at 20 mg/kg/day in females at exposure margins in females of 1.7- and 4.4-fold for GS-9131 and GS-9148, respectively. The increased incidence and/or severity in this study may have been a stress-related change. There was no evidence of lymphoid depletion in the spleen or lymph nodes in dogs. In rats, lymphoid depletion in the spleen was observed in a 4-week immunotoxicity study, but was not noted in 4-week and 26-week repeat dose toxicity studies, and there were no notable changes in peripheral blood immunophenotyping in the 4-week rat study. In the immunotoxicity study, immunosuppressive effects (decreased response to keyhole limpet hemocyanin [KLH] immunization) were seen in male rats at ≥ 100 mg/kg/day; similar functional changes were not seen in females at GS-9148 exposures margins over 18-fold.

Reversible, hematopoietic effects were observed in a 26-week rat study with slightly lower mean values for red blood cells (RBC), hemoglobin (Hb) and hematocrit (HCT) in 225 mg/kg/day males and females, corresponding to 13- and 21-fold GS-9148 margins, respectively. In dogs, slightly lower RBC, Hb, and HCT values were observed at 20 mg/kg/day with dose-dependent decreases in total leukocyte, neutrophil and lymphocyte counts evident at ≥ 10 mg/kg/day, and decreases in monocyte and eosinophil counts and mean myeloid:erythroid (M:E) ratios occurring primarily at 20 mg/kg/day. The lower lymphocyte and eosinophil counts correlated with thymic

lymphoid depletion. Clinical studies have not revealed any clinically-relevant hematology changes after single or multiple dosing with GS-9131. Standard hematology evaluation should be adequate to monitor for potential GS-9131 effects.

In 13-week mouse and 26-week rat studies, and a 39-week repeat-dose toxicology study in cynomolgus monkeys, mortality was noted at correlating exposure margins of 9.1- and 21-fold for GS-9148 in mouse and rat studies, respectively, and 0.5- and 1.6-fold for GS-9131 and GS-9148, respectively in the monkey study. In all three studies, no specified target organs of toxicity were noted at the high dose levels associated with mortality. Specifically, in the 13-week mouse study, the high dose group (300 mg/kg/day) was terminated early (Day 32) due to mortality. In the 26-week rat study, mortality was observed in 3 of 15 females (Days 49, 171, and 172) in the high dose group (225 mg/kg/day). Finally, in the 39-week monkey study, one high dose group (30 mg/kg/day) female was found dead (Day 85). The relationship of test article to mortality observed in repeat-dose toxicology studies at high dose levels is unclear.

Effects on fertility were noted female rats at 300 mg/kg/day. At the 100 mg/kg/day NOAEL, exposures were 5.3-fold for GS-9148 compared to projected clinical exposures at the GS-9131 180 mg dose. In embryo-fetal development studies in pregnant rats and rabbits, there were no effects on embryo-fetal development.

Further information is available in the current version of the IB for GS-9131.

1.2.3. Clinical Trials of GS-9131

Clinical trials of GS-9131 include:

GS-US-180-0101, a Phase 1 randomized, double-blind, placebo-controlled, dose-escalation study to evaluate the safety, tolerability, and PK of single doses of GS-9131 (10 mg fasted, 30 mg fasted, and 30 mg fed) in healthy subjects (completed).

GS-US-180-0103, a Phase 1, randomized, open-label, multiple-dose, six-sequence, three-way crossover study evaluating the PK drug interaction of GS-9131 30 mg once daily (QD) and Truvada (emtricitabine/tenofovir disoproxil fumarate [FTC/TDF] 200 mg/300 mg fixed-dose combination [FDC] tablet) QD when administered together, compared to their administration alone (completed).

GS-US-180-4149, a Phase 1 study to evaluate the PK of GS-9131 in combination with cobicistat-boosted darunavir plus bictegravir, a ritonavir-boosted protease inhibitor, or tenofovir alafenamide (ongoing).

GS-US-180-0104, a Phase1/2 study of the safety, PK and antiviral activity of GS-9131 in ARV-naïve, HIV-1 infected subjects (completed).

Further information on completed Phase 1 studies is available in the current version of the IB for GS-9131.

1.2.3.1. Study GS-US-180-4149

Study GS-US-180-4149 is an ongoing Phase 1, randomized, open-label, multiple-dose, multi-cohort, study evaluating the PK of GS-9131 in combination with DRV/COBI (800/150 mg) plus BIC (50 mg), ATV/RTV (300/100 mg), LPV/RTV (800/200 mg), or TAF (25 mg).

Subjects in Cohort 1 received 10 days of GS-9131 (10 mg) in combination with DRV/COBI (800/150 mg) plus BIC (50 mg) (Treatment A; N=24). Subjects in Cohort 2 received 10 days of GS-9131 (10 mg) alone (Treatment B; N=24).

Subjects in Cohort 3 received 10 days of GS-9131 (60 mg) alone (Treatment C; N=24) or in combination with DRV/COBI (800/150 mg) (Treatment D; N=24).

Subjects in Cohort 4 received 10 days of GS-9131 (30 mg) alone (Treatment F; N= 11), in combination with ATV+RTV (300/100 mg; Treatment E; N=12), or in combination with LPV/RTV (800/200 mg; Treatment G; N=10).

Subjects in Cohort 5 received 14 days of either GS-9131 (60 mg) alone (Treatment H; N= 24), followed by 14 day of GS-9131 (60 mg) plus TAF (25 mg) (Treatment I; N=24), or TAF (25 mg) alone (Treatment J; N= 29), followed by 14 day of GS-9131 (60 mg) plus TAF (25 mg) (Treatment I; N=29).

All doses were administered in the morning under fed conditions. Blood samples were drawn on the last day of each treatment to characterize PK of GS-9131 and its metabolite, GS-9148, in plasma, and GS-9148-DP in PBMCs.

1.2.3.1.1. GS-9131

GS-9131 exposures were lower when GS-9131 (10, 30 or 60 mg) was coadministered with DRV/COBI plus BIC, or LPV/RTV (decreases in GS-9131 AUC_{tau} ranged from 28% to 46%; similar changes were observed with C_{max}). Minimal changes in GS-9131 exposure were observed upon coadministration with ATV+RTV or with TAF (Table 4).

1.2.3.1.2. GS-9148

With respect to GS-9148, higher exposures were observed upon coadministration of GS-9131 (10, 30 or 60 mg) with all boosted-PI regimens tested (COBI-boosted DRV plus BIC, ATV+RTV or LPV/RTV). GS-9148 AUC_{tau} increased to a greater extent when GS-9131 was coadministered with either DRV/co plus BIC at the GS-9131 60 mg dose (AUC_{tau} was 436% higher) or with LPV/RTV or ATV+RTV, respectively, at the GS-9131 30 mg dose (AUC_{tau} was 314% and 236% higher, respectively) compared to the increase in GS-9148 exposures observed at the GS-9131 10 mg dose coadministered with DRV/co plus BIC (147% increase in AUC_{tau}). Changes in GS-9148 C_{max} and C_{tau} were consistent with changes in AUC_{tau}. Minimal changes in GS-9148 exposure were observed upon coadministration with TAF (Table 2).

Table 2. Study GS-US-180-4149 Preliminary Plasma PK Data from Cohorts 1-5

PK parameter Mean (%CV)	Cohort 1 DRV/COBI + BIC+GS-9131 (10 mg; Test) N=24	Cohort 2 GS-9131 (10 mg; Reference) N=24	GLSM Ratio% (90%CI) (Test/Reference)
GS-9131			
AUC_{tau} (hr*ng/mL)	55.7 (20.1)[a]	79.2 (27.5)[b]	71.7 (61.9, 83.0)
C_{max} (ng/mL)	54.9 (54.9)	69.9 (48.8)	77.7 (61.1, 98.7)
GS-9148			
AUC_{tau} (hr*ng/mL)	536 (16.6)	218 (19.3)	247 (226, 269)
C_{max} (ng/mL)	37.9 (14.7)	16.4 (24.3)	235 (214, 258)
C_{tau} (ng/mL)	14.5 (19.2) (66.8)	6.90 (66.8)	227 (196, 263)
	Cohort 3 DRV/COBI + BIC+GS-9131 (60 mg; Test) N=23	**Cohort 3 GS-9131 (60 mg; Reference) N=24**	**GLSM Ratio% (90%CI) (Test/Reference)**
GS-9131			
AUC_{tau} (hr*ng/mL)	419 (23.3)[b]	796 (31.4)	53.9 (48.2, 60.2)
C_{max} (ng/mL)	353 (48.0)	645 (40.9)	53.1 (42.6, 66.0)
GS-9148			
AUC_{tau} (hr*ng/mL)	3570 (13.7)	675 (22.5)	536 (498, 577)
C_{max} (ng/mL)	237 (13.7)	52.3 (21.7)	459 (423, 499)
C_{tau} (ng/mL)	103 (17.1)	16.8 (23.0)	615 (572, 662)
	Cohort 4 LPV/RTV +GS-9131 (30 mg; Test) N=10	**Cohort 4 GS-9131 (30 mg; Reference) N=11**	**GLSM Ratio% (90%CI) (Test/Reference)**
GS-9131			
AUC_{tau} (hr*ng/mL)	240 (44.6)[c]	415 (51.5)	58.3 (43.9, 77.5)
C_{max} (ng/mL)	326 (61.2)	385 (80.0)	83.5 (59.2, 118)
GS-9148			
AUC_{tau} (hr*ng/mL)	1900 (22.1)	470 (33.7)	414 (349, 492)
C_{max} (ng/mL)	127 (15.6)	35.1 (29.0)	370 (316, 432)
C_{tau} (ng/mL)	48.4 (25.4)	12.9 (35.9)	385 (318, 467)

	Cohort 4 ATV+RTV +GS-9131 (30 mg; Test) N=12	**Cohort 4 GS-9131 (30 mg; Reference) N=11**	**GLSM Ratio% (90%CI) (Test/Reference)**
GS-9131			
AUC_{tau} (hr*ng/mL)	320 (29.2)	415 (51.5)	84.5 (72.2, 98.9)
C_{max} (ng/mL)	346 (75.9)	385 (80.0)	98.0 (86.1, 111)
GS-9148			
AUC_{tau} (hr*ng/mL)	1530 (18.1)	470 (33.7)	336 (292, 387)
C_{max} (ng/mL)	112 (17.6)	35.1 (29.0)	328 (288, 374)
C_{tau} (ng/mL)	40.4 (18.0)	12.9 (35.9)	326 (277, 383)
	Cohort 5 TAF +GS-9131 (60 mg; Test) N=24	**Cohort 5 GS-9131 (60 mg; Reference) N=24**	**GLSM Ratio% (90%CI) (Test/Reference)**
GS-9131			
AUC_{tau} (hr*ng/mL)	854 (42.5)	865 (40.3)	98.8 (92.6, 105)
C_{max} (ng/mL)	701 (44.3)	636 (33.4)	107 (95.9, 119)
GS-9148			
AUC_{tau} (hr*ng/mL)	814 (19.9)	744 (19.4)	109 (107, 112)
C_{max} (ng/mL)	60.3 (16.8)	55.3 (15.0)	109 (106, 112)
C_{tau} (ng/mL)	22.0 (21.7)	20.1 (21.7)	109 (106, 113)

Data are presented to 3 significant figures
a N=16
b N = 21
c N= 9

1.2.3.1.3. GS-9148-DP

Exposures (AUC_{0-24} and C_{24}) of PBMC-associated GS-9148-DP following once-daily dosing of GS-9131 alone (10, 30 or 60 mg) or in combination with a boosted PI regimen (DRV/COBI plus BIC, LPV/RTV or ATV+RTV) for 10 days, or in combination with TAF for 14 days, are presented in Table 3. The PBMC-associated GS-9148-DP concentrations at the GS-9131 30 mg dose in this study were similar to those observed following administration of GS-9131 30 mg once daily for 10 days in the POC study in treatment-naïve HIV-infected subjects, in which a 1.03 log_{10} median reduction in HIV-RNA was observed (Study GS-US-180-0104).

Table 3. Study GS-US-180-4149 Preliminary PBMC PK Data from Cohorts 1-5

GS-9148-DP PK parameter Mean (%CV)	Cohort 1 DRV/COBI + BIC+GS-9131 (10 mg) N=24	Cohort 2 GS-9131 (10 mg) N=24
AUC_{0-24} (uM*hr)	40.4 (33.0)	30.1 (27.1)
C_{24} (uM)	1.48 (37.5)	0.95 (28.2)
	Cohort 3 DRV/COBI + BIC+GS-9131 (60 mg) N=23	**Cohort 3 GS-9131 (60 mg) N=23**
AUC_{0-24} (uM*hr)	179 (53.3)	124 (46.4)[a]
C_{24} (uM)	8.35 (64.8)	5.26 (52.3)
	Cohort 4 LPV/RTV +GS-9131 (30 mg) N=10	**Cohort 4 GS-9131 (30 mg) N=11**
AUC_{0-24} (uM*hr)	70.8 (43.0)	91.4 (27.3)
C_{24} (uM)	2.00 (28.7)	3.25 (32.0)
	Cohort 4 ATV+RTV +GS-9131 (30 mg) N=12	**Cohort 4 GS-9131 (30 mg) N=11**
AUC_{0-24} (uM*hr)	138 (29.7)	91.4 (27.3)
C_{24} (uM)	5.34 (29.7)	3.25 (32.0)
	Cohort 5 TAF +GS-9131 (60 mg) N=24	**Cohort 5 GS-9131 60 mg) N=24**
AUC_{0-24} (uM*hr)	188 (49.0)	212 (78.2)
C_{24} (uM)	5.83 (50.5)	6.76 (56.9)

Data are presented to 3 significant figures
a N=23

1.2.3.1.4. BIC and DRV/COBI

Preliminary data demonstrated that BIC (50 mg) exposure following co-administration with DRV/COBI (800/150 mg) and GS-9131 (10 mg) in Cohort 1 was within the range of BIC (75 mg) exposure previously observed in Phase 1 and 2 studies (Studies GS-US-141-1233, GS-US-141-1475, GS-US-141-1478, GS-US-141-1479, GS-US-141-1480, GS-141-1485, GS-US-141-1487, and GS-US-311-1790). Exposures of DRV and COBI were consistent with historical data {PREZCOBIX 2018}.

1.2.3.1.5. TAF, TFV and TFV-DP

Preliminary TAF plasma exposures were higher following coadministration with GS-9131 60 mg (AUC_{tau} and C_{max} were 69% and 17% higher, respectively) as compared to TAF alone, these TAF exposures were within the range of TAF exposures for which safety and efficacy has been established {Genvoya 2018}.

Preliminary plasma exposures of TFV were lower following coadministration with GS-9131 60 mg (AUC_{tau} and C_{max} were 51% and 57% lower, respectively) as compared to TAF alone; as TFV is an inactive metabolite, this change was not considered clinically meaningful.

Preliminary exposures (AUC) of TFV-DP in PBMCs were 135% higher upon coadministration with GS-9131 60 mg with TAF compared with TAF alone. Values were within the range of those observed in historical studies of approved FTC/TAF containing products (Studies GS-US-311-1089, GS-US-292-0112, GS-US-292-1825, GS-US-380-4017)

1.2.3.1.6. Preliminary safety

GS-9131 was generally well tolerated at the doses evaluated. Preliminary data indicate that AEs were mild to moderate in severity. There were no deaths, pregnancies, Grade 3 or 4 AEs or SAEs. One subject in Cohort 4 experienced study drug related Grade 2 AEs of pruritus and dermatitis while receiving GS-9131 30 mg coadministered with Reyataz® and discontinued study drugs.

1.2.3.2. Study GS-US-180-0104

Study GS-US-180-0104 was a single-center, randomized, double-blind, multiple-dose, placebo-controlled study evaluating the antiviral activity, safety, and PK of GS-9131 in ARV-naive subjects chronically infected with HIV-1. Eligible subjects were randomized in a 2:1 ratio to receive GS-9131 30 mg or matching placebo for 10 consecutive days. Eighteen male subjects were randomized and treated and all subjects completed 10 days of treatment.

Derived PK parameters of GS-9131 and GS-9148 after single dose administration of GS-9131 were similar to values seen previously in Study GS-US-180-0101. GS-9131 was rapidly hydrolyzed and exhibited a short plasma $t_{1/2}$, while GS-9148 exhibited a mean $t_{1/2}$ of > 20 hours {reference IB}. GS-9148 exhibited near-linear pharmacokinetics, with accumulation ratios of nearly one (AUC geometric mean ratio was 79.35 [90% confidence interval: 70.42, 89.41]) {reference IB}. In Study GS-US-180-0104, single and multiple doses of GS-9131 resulted in high concentrations of the active antiretroviral metabolite, GS-9148-DP, in PBMCs (Table 4). PK parameters of GS-9131 and GS-9148 after 10 days multiple dose administration of GS-9131 (30 mg) are presented in Table 1.

Table 4. Study GS-US-180-0104 Multiple Dose PK Data

PK parameter[a] Mean (%CV)	GS-9131 30 mg (N=12)
GS-9131	
AUC_{tau} (hr*ng/mL)	250 (25.7)
C_{max} (ng/mL)	386 (32.2)
GS-9148	
AUC_{tau} (hr*ng/mL)	411 (23.3)
C_{max} (ng/mL)	47.3 (18.4)
GS-9148-DP	
AUC_{0-24} (uM*hr)	100 (51.0)
C_{24} (uM)	5.29 (49.0)

a Values are presented to 3 significant figures.

The primary efficacy endpoint was the maximum reduction from baseline in HIV-1 RNA (log_{10} copies/mL) on measurements taken between Days 2 to 11. HIV-1 RNA levels in the GS-9131 group steadily decreased over the dosing period, and the maximum reduction from baseline in HIV-1 RNA (log_{10} copies/mL) up to Day 11 (primary endpoint) was significantly greater in the GS-9131 group (median [IQR] -1.03 [-1.37, -0.76] copies/mL) than in the placebo group (median [IQR] -0.10 [-0.43, -0.05] copies/mL) ($p = 0.001$). Seven of twelve (58.3%) subjects in the GS-9131 group compared to zero of six subjects in the placebo group achieved at least a 1.0 log_{10} decrease from baseline in HIV-1 RNA from Days 2 to 11 ($p = 0.038$).

Changes from baseline in CD4 counts and percentages were not significantly different between the treatment groups.

Resistance analyses showed no evidence of primary drug resistance mutations at baseline. Overall, no RT mutations associated with NRTI or GS-9131 resistance developed in subjects treated with GS-9131. In addition, HIV-1 showed full phenotypic susceptibility to GS-9131 from baseline through Day 11 for subjects in the GS-9131 group.

The safety findings demonstrated that GS-9131 was generally well tolerated. All AEs were mild to moderate in severity. No treatment-related AEs ≥ Grade 3, SAEs, pregnancies, deaths, or AEs leading to study drug interruption or premature study drug discontinuation were reported. Four subjects (1 [8.3%] in GS-9131 group, 3 [50%] in placebo group) had treatment-emergent Grade 3 or 4 laboratory abnormalities; none were considered related to study drug.

1.2.3.3. Study GS-US-442-4148

Preliminary data from Sentinel Cohort 1 in Table 5 indicate that GS-9131, GS-9148, and GS-9148-DP exposure in HIV-infected subjects following administration of GS-9131 60 mg is approximately 2-fold higher than that observed in HIV-infected subjects receiving GS-9131 30 mg (Study GS-US-180-0104; Table 4), and similar to that observed in healthy volunteers receiving GS-9131 60 mg (Study GS-US-180-4149; Table 2).

Table 5. Study GS-US-442-4148 Preliminary PK Data

PK parameter[a] Mean (%CV)	GS-9131 60 mg (N=11)
GS-9131	
AUC_{tau} (hr*ng/mL)	599 (65.9)
C_{max} (ng/mL)	777 (72.6)
GS-9148	
AUC_{tau} (hr*ng/mL)	955 (51.3)
C_{max} (ng/mL)	69.3 (46.9)
GS-9148-DP	
AUC_{0-24} (uM*hr)	202 (50.0)
C_{24} (uM)	7.70 (68.9)

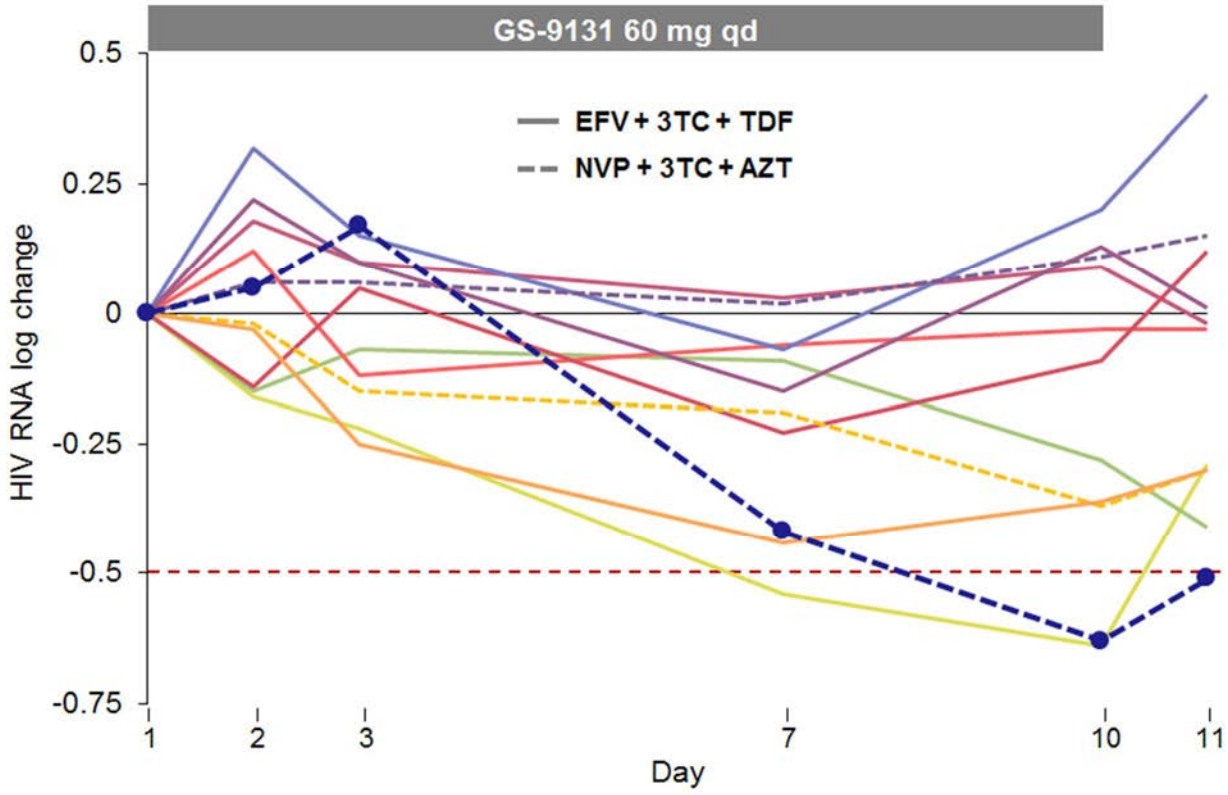
a Values are presented to 3 significant figures.

1.2.3.3.1.1. Clinical Results from the GS-9131 60 mg Sentinel Cohort

In Study GS-US-442-4148, clinical data from the Sentinel Cohort showed 2 of 11 subjects experienced a > 0.5 log decline in viral load from baseline and an additional 3 of 11 subjects experienced a > 0.3 log decline in viral load from baseline (Figure 1). Viruses from all 11 subjects were phenotypically sensitive to GS-9148 at Day 1 and Day 11 and there was no development of new HIV resistance mutations. There were no changes in genotypic or phenotypic sensitivity to NRTIs, NNRTIs, or PIs observed in these subjects. One subject progressed to Part 2 of the study and achieved virologic suppression (< 50 copies/ml) on the regimen of GS-9131(60 mg)+ BIC (30 mg) + DRV (800 mg)+ RTV (100 mg).

GS-9131 60 mg was generally well tolerated with Grade 3 cellulitis reported for 1 subject and considered not related to study drug. No subjects had Grade 3 or 4 laboratory abnormalities associated with GS-9131.

Figure 1. Study GS-US-442-4148: Changes in Viral Load by Subject and Failing ARV Regimen in the Sentinel Cohort



1.3. Bictegravir

1.3.1. General Information

Bictegravir (BIC, previously known as GS-9883), is a potent inhibitor of HIV-1 integrase. Antiviral testing has shown that BIC is active against a broad panel of HIV-1 viral lab strains and clinical isolates. Bictegravir is fully active against a panel of mutant viruses with resistance to NRTIs, NNRTIs, and PIs.

1.3.2. Nonclinical Pharmacology, Pharmacokinetics and Toxicology

The volume of distribution of BIC ranged between 0.09 and 0.22 L/kg in the preclinical species, which indicates that the distribution of BIC is limited to the extracellular compartment due to its high binding to plasma proteins. The projected half-life of BIC in humans is approximately 20 hours based upon the estimates of clearance and volume of distribution.

The oral toxicity of BIC has been studied in transgenic mice, rats, and monkeys for treatment periods up to 39 weeks. In a 39-week repeat dose chronic toxicology study in monkeys, hepatobiliary toxicity at the high dose of 1000 mg/kg/day was the only notable adverse finding at

BIC plasma exposures that were 16-fold higher than those observed in patients at a 50 mg BIC dose. The effects were partially reversible after a four week period of non-exposure (recovery). No toxicity was observed at the mid-dose of 200 mg/kg/day which provided a margin of exposure 7-fold greater than the clinical exposure. No target organs were identified following repeat oral administration of 1000 mg/kg/day BIC in cynomolgus monkeys for up to 13 weeks. No adverse findings were noted in transgenic mouse or rat repeat dose toxicology studies up to 26 weeks dosing duration with exposure margins at the NOAELs of ≥ 18-fold the BIC plasma exposure at the clinical dose of 50 mg in the BIC/FTC/TAF FDC.

For more information on the preclinical studies of BIC, please refer to the BIC IB.

1.3.3. Clinical Studies of Bictegravir

To date, 23 Phase 1, 2 or 3 clinical studies have been completed or are ongoing in which 568 healthy subjects and over 1600 HIV-infected subjects have been dosed with BIC, either as a single agent or as BIC/FTC/TAF. Clinical trials entailing the use of BIC include:

- GS-US-141-1218, a Phase 1, double blind, randomized, placebo-controlled, first-in-human, single- and multiple-ascending dose study evaluating the safety, tolerability, and PK of oral GS-9883 (BIC) in healthy subjects and a randomized, open label, 2-cohort, 3-period, crossover, PK study evaluating the drug interaction potential between FTC/TAF FDC tablet and GS-9883 in healthy subjects (completed)

- GS-US-141-1219, a Phase 1b, randomized, double-blinded, sequential cohort placebo controlled study of the safety, PK, and antiviral activity of GS-9883 (5 mg, 25 mg, 50 mg, 100 mg) in HIV-1 infected subjects (completed)

- GS-US-141-1233, a Phase 1, open-label, two-cohort, multiple-period, fixed sequence, crossover study to evaluate 1) the relative bioavailability of two GS-9883/FTC/TAF (75/200/25 mg and 50/200/25 mg) FDC tablets versus a GS-9883 (75 mg) tablet and an FTC/TAF (200/25 mg) FDC tablet administered simultaneously and 2) the effect of food on the PK of GS-9883, FTC and TAF when administered as GS-9883/FTC/TAF (75/200/25 mg and 50/200/25 mg) FDC (completed)

- GS-US-141-1478, a Phase 1, open-label, parallel-group, adaptive single dose study to evaluate the PK of GS-9883 in subjects with normal and impaired hepatic function (completed)

- GS-US-141-1479, a Phase 1, open-label, parallel-group, adaptive single dose study to evaluate the PK of GS-9883 in subjects with normal and impaired renal function (completed)

- GS-US-141-1480, a Phase 1, partially-blinded, randomized, placebo- and positive-controlled study to evaluate the effect of GS-9883 on the QT/QTc interval in healthy subjects (completed)

- GS-US-141-1481, a Phase 1 study to evaluate the PK, metabolism, and excretion of GS-9883 in healthy subjects (completed)

- GS-US-141-1485, a Phase 1 adaptive study to evaluate transporter, CYP-mediated and UGT1A1 drug-drug interactions between GS-9883 and probe drugs (completed)

- GS-US-141-1487, a Phase 1, randomized, blinded, placebo-controlled Phase 1 study evaluating the effect of GS-9883 on renal function as assessed by markers of glomerular filtration rate (completed)

- GS-US-311-1790, a Phase 1, randomized, open-label, drug interaction study evaluating the effect of FTC/TAF FDC tablet or GS-9883 on the PK of a representative hormonal contraceptive medication, norgestimate/ethinyl estradiol (completed)

- GS-US-141-1475, a Phase 2, randomized, double-blinded study of the safety and efficacy of GS-9883 + FTC/TAF versus dolutegravir + FTC/TAF in HIV-1 infected, ART-naive adults (ongoing)

- GS-US-380-1489, a Phase 3, randomized, double-blind study to evaluate the safety and efficacy of GS-9883/FTC/TAF versus Abacavir (ABC)/Dolutegravir (DTG)/Lamivudine (3TC) in HIV-1 infected, ART-naïve adults (ongoing)

- GS-US-380-1490, a Phase 3, randomized, double-blind study to evaluate the safety and efficacy of GS-9883/FTC/TAF versus DTG + FTC/TAF in HIV-1 infected, ART-naïve adults (ongoing)

- GS-US-380-1844, a Phase 3, randomized, double-blind study to evaluate the safety and efficacy of switching from a regimen of DTG and ABC/3TC, or an FDC of ABC/DTG/3TC to an FDC of GS-9883/FTC/TAF in HIV-1 infected subjects who are virologically suppressed (ongoing)

- GS-US-380-1878, a Phase 3, randomized, open-label study to evaluate the safety and efficacy of switching from regimens consisting of boosted Atazanavir or DRV plus either FTC/TFV or ABC/3TC to GS-9883/FTC/TAF in virologically suppressed HIV-1 infected adults (ongoing)

- GS-US-380-1961, a Phase 3, randomized, open label study to evaluate the safety and efficacy of switching to a FDC of GS-9883/FTC/TAF from elvitegravir (EVG)/COBI/FTC/TAF, EVG/COBI/FTC/TDF or atazanavir + ritonavir + FTC/TDF in virologically suppressed HIV-1 infected women (ongoing)

- GS-US-380-1474, a Phase 2/3, open-label study of the PK, safety, and antiviral activity of the GS-9883/FTC/TAF FDC in HIV-1 infected virologically suppressed adolescents and children (ongoing)

Please refer to the BIC for further information about these studies.

1.3.3.1. Study GS-US-141-1219 (Phase 1b Proof of Concept)

The first HIV-1 infected human subjects were dosed in the fasted state with 10 days of BIC in Study GS-US-141-1219. A total of 23 subjects were randomized 4:1 to receive BIC or placebo to match at doses of 5 mg, 25 mg, 50 mg, and 100 mg QD for 10 days; 20 subjects received study treatment and completed the study.

Mean HIV-1 RNA change on Day 11 was -2.08 $\log_{10}$ copies/mL in the 25 mg cohort, -2.06 $\log_{10}$ copies/mL in the 50 mg cohort, and -2.43 $\log_{10}$ copies/mL in the 100 mg cohort. Time weighted average change from baseline at Day 11 (DAVG11) was -0.92 $\log_{10}$ copies/mL in the 5 mg cohort, -1.33 $\log_{10}$ copies/mL in the 25 mg cohort, -1.37 $\log_{10}$ copies/mL in the 50 mg cohort and -1.61 $\log_{10}$ copies/mL in the 100 mg cohort. Viral suppression (HIV-1 RNA < 50 copies/mL) was not achieved by the end of the study (Day 17) for 1 subject (25.0%) in the BIC 50 mg group and 2 subjects (50%) in the BIC 100 mg group. No subject developed a primary INSTI-R substitution.

Bictegravir was generally well tolerated at the doses evaluated. No deaths or pregnancies were reported. No Grade 3 or 4 AEs, SAEs, or AEs leading to discontinuation of study drug were reported in any cohort. There was no increase in the incidence of AEs with increasing doses of BIC. The majority of AEs were considered by the investigator to be not related to study drug.

The majority of laboratory abnormalities were Grade 1 or Grade 2 in severity. No Grade 3 treatment-emergent laboratory abnormalities were observed. One subject had a Grade 4 laboratory abnormality (elevated creatine phosphokinase, GS-9883 5 mg treatment group), which was also reported as an AE (Grade 2 severity, not considered related to study drug). Median serum creatinine changes at Day 10 were: 0.05 mg/dL (5 mg), 0.04 mg/dL (25 mg), 0.06 mg/dL (50 mg), and 0.15 mg/dL (100 mg). These changes in serum creatinine appeared to be transient and returned close to baseline values on discontinuation of study drug.

1.3.3.2. Summary of Phase 2 Study GS-US-141-1475

Study GS-US-141-1475 is an ongoing Phase 2, randomized, double-blind, multicenter, active-controlled study to assess the safety and efficacy of a regimen containing BIC + FTC/TAF versus DTG + FTC/TAF in HIV-infected, ART-naive adult subjects. Ninety-eight eligible subjects were randomized in a 2:1 ratio to BIC + FTC/TAF (n=65) and DTG + FTC/TAF group (n=33), stratified by HIV-1 RNA level (≤ 100,000 copies/mL, > 100,000 copies/mL to ≤ 400,000 copies/mL, or > 400,000 copies/mL) at screening.

At the time of the Week 24 data analysis, 2 subjects (2.0%) had prematurely discontinued from the study, 1 in each treatment group; both subjects were lost to follow-up. At Week 48, 2 additional subjects in each treatment group prematurely discontinued the study. In the BIC + FTC/TAF group, one subject discontinued due to an AE of urticaria and one subject withdrew consent at Week 48. In the DTG + FTC/TAF group, 2 subjects discontinued due to study drug non-compliance.

Virologic success at Weeks 12, 24 and 48 were assessed using the US FDA-defined snapshot algorithm, defined as plasma HIV-1 RNA < 50 copies/mL. At each time point, virologic success was high and similar between the 2 treatment groups as follows: Week 12 BIC + FTC/TAF

93.8%, DTG + FTC/TAF 93.9% (stratum-adjusted difference in percentages: −1.3%; 95% CI: −12.9% to 10.2%; p = 0.79); Week 24 BIC + FTC/TAF 95.4%, DTG + FTC/TAF 93.9% (1.0%; 95% CI: −10.7% to 12.7%; p = 0.84); Week 48 BIC + FTC/TAF 96.9%, DTG + FTC/TAF 90.9% (6.4%; 95% CI: -6.4% to 18.8%; p = 0.17). Through Week 48, there was no virologic resistance seen in any subject treated with BIC + FTC/TAF. Following initiation of study drug, the increases from baseline in CD4 cell count were similar between treatment groups.

Both BIC + FTC/TAF and DTG + FTC/TAF were generally well-tolerated through 48 weeks of treatment. The most commonly reported treatment-emergent AEs were diarrhea and headache (7.7% each) in the BIC + FTC/TAF group and nausea (12.1%) and diarrhea (9.1%) in the DTG + FTC/TAF group. Three subjects experienced SAEs, 1 of which was also a Grade 3 AE; none of these events were considered related to study drug by the investigator, or led to study drug discontinuation. There was one Grade 3AE (urticaria) that led to study drug discontinuation in the BIC + FTC/TAF group. There were no other Grade 3 or 4 AEs, and no deaths, pregnancies, or AEs leading to premature study drug discontinuation reported. The percentage of subjects with at least 1 treatment-emergent laboratory abnormality was similar between treatment groups. The majority of treatment-emergent laboratory abnormalities were Grade 1 or 2 in severity. There were similar increases from baseline in serum creatinine in both treatment groups at Week 48.

1.4. Tenofovir Alafenamide (TAF)

Tenofovir alafenamide (TAF) is a second generation oral prodrug of tenofovir (TFV), a nucleotide analog that inhibits HIV-1 reverse transcription. Tenofovir is metabolized intracellularly to the active metabolite, tenofovir diphosphate (TFV-DP), a competitive inhibitor of HIV-1 reverse transcriptase (RT) that terminates the elongation of the viral DNA chain. The intracellular metabolism of TAF and TFV are consistent with the 600-fold enhancement in anti-HIV activity in cell culture of TAF over TFV. Tenofovir alafenamide is also part of the approved fixed dose combinations (FDCs) of Genvoya® (elvitegravir (EVG)/cobicistat (COBI)/FTC/TAF), Descovy® (FTC/TAF), Odefsey® (FTC/rilpivirine (RPV)/TAF), and Biktarvy (BIC/FTC/TAF) for the treatment of HIV-1 infection. Additionally, TAF (Vemlidy®) is approved for the treatment of chronic hepatitis B virus (HBV) infection.

Please refer to the TAF Investigator Brochure for further information.

1.5. Darunavir (DRV, Prezista®)

Prezista® (darunavir (DRV)), is an HIV-1 protease inhibitor and is indicated for the treatment of HIV-1 infection in adult patients in combination with other antiretroviral agents. In patients with no DRV resistance associated mutations, the recommended dosage, is 800 mg DRV taken in combination with and 100 mg of Norvir® (ritonavir (RTV)) taken once daily with food.

The most common clinical adverse drug reactions to Prezista/ritonavir (incidence greater than or equal to 5%) of at least moderate intensity (greater than or equal to Grade 2) were diarrhea, nausea, rash, headache, abdominal pain and vomiting. Rare instances of severe hepatotoxicity

were observed, primarily in patients with pre-existing liver dysfunction. Severe skin reactions accompanied by fever and/or elevations in transaminases were reported in 0.4% of subjects, and Stevens-Johnson syndrome occurred in less than 0.1%.

Further information regarding DRV is available in the Prezista® Package Insert.

1.6. Ritonavir (RTV, Norvir®)

Ritonavir is a pharmacoenhancer with CYP3A inhibitory activity that boosts DRV systemic exposures. In addition to the common adverse reactions noted in combination with DRV, potentially serious and/or life-threatening adverse events can occur due to drug-drug interactions, hepatotoxicity, or pancreatitis. Other serious reactions include severe skin reactions, heart block, lipid elevations, hyperglycemia, or body fat changes. Further information regarding RTV is available in the Norvir® Package Insert.

1.7. Rationale for This Study

The United States Department of Health and Human Services (US DHHS) Guidelines (2016) {Panel on Antiretroviral Guidelines for Adults and Adolescents 2016} and World Health Organization (WHO) Guidelines (2016) {World Health Organization (WHO) 2016} outline the approach to treatment failure in both resource-rich and resource-limited settings, respectively. Both guidelines make it clear that the addition of 2-3 antiretroviral agents with anticipated full antiviral activity should be used {Panel on Antiretroviral Guidelines for Adults and Adolescents 2016, World Health Organization (WHO) 2016}.

Gilead Sciences' novel drug GS-9131, a prodrug of the novel adenine nucleotide analog GS-9148, is a potent inhibitor of HIV-1 in primary human peripheral blood mononuclear cells (PBMCs), CD4 T-lymphocytes, and macrophages. GS-9131 has exhibited a favorable resistance profile in *in vitro* studies that is distinct from that of most marketed N(t)RTIs. GS-9131 is anticipated to provide full activity against many NRTI mutations. In addition, GS-9131 has demonstrated a low potential for renal and mitochondrial toxicity, an important advantage over currently approved N(t)RTIs.

Extensive phenotypic resistance profiling of GS-9131 (and GS-9148) with multiple NRTI-resistant patient-derived HIV-1 strains and site-directed mutants resulted in a resistance profile superior to any marketed NRTI. GS-9131 retained full activity against viruses with M184V, K65R, or L74V mutations and viruses with 4 to 6 TAMs with or without the T69 insertion mutation. In vitro data demonstrate a high resistance barrier based on delayed resistance development and either low-level resistance or high-level resistance with replication-limiting fitness defects. Ongoing in vitro selections with multidrug-resistant (MDR) NRTI mutants of HIV (3 TAMs or K65R) with GS-9131 have found no additional resistance development through at least 8 weeks of culture.

The primary objective of this study is to evaluate the antiviral efficacy of GS-9131 as functional monotherapy in subjects who are failing their existing antiretroviral regimen containing NRTIs and an NNRTI. In vitro evidence supports GS-9131 activity against NRTI resistant viruses, but the efficacy of GS-9131 against such viruses has not yet been demonstrated in human subjects.

Virologic response was low following administration of GS-9131 60 mg for 10 days in the Sentinel Cohort 1 of this study (GS-US-442-4148), which may be attributed to suboptimal dosing and duration. The prodrugs of NRTIs require metabolic modification to release the prodrug and phosphorylation to achieve the active metabolite, and a longer duration of time (up to 14 days) is required for NRTIs in order to quantify maximal viral load decline {Barditch-Crovo 2001, Squires 2003}. In order to optimize intracellular loading and processing in HIV-1 infected target cells, virologic response to GS-9131 in TE HIV-1 infected subjects will be assessed in a second Sentinel Cohort of GS-9131 180 mg once daily for14 days. Subjects from this second sentinel cohort who successfully complete the functional monotherapy, defined as a >0.5 log_{10} reduction in plasma HIV-1 RNA from baseline, will initiate a regimen of GS-9131, BIC, and TAF for 24 weeks. Bictegravir is a potent INSTI with a high resistance barrier that will represent a new class of ARV for this TE population. TAF has safety advantages over tenofovir disoproxil fumarate and delivers higher drug levels to cells that may translate to improved antiviral activity against HIV-1 with NRTI resistance. BIC and TAF are approved components of Biktarvy (BIC/FTC/TAF), a complete regimen for the treatment of HIV-1 infection.

1.8. Rationale for the Dose Selection

1.8.1. GS-9131

GS-9131 is a nucleotide reverse transcriptase inhibitor (NtRTI) prodrug, a class that includes tenofovir alafenamide (TAF). In the TAF study (Study GS-US-120-0104) of similar duration and design to Study GS-US-180-0104, decreases in HIV-1 RNA of -1.08, -1.46, and -1.73 log_{10} copies/mL were observed on Day 10, at TAF doses of 8 mg, 25 mg, and 40 mg QD, respectively {Ruane 2013}. Additionally, in subjects treated with FTC, a nucleoside reverse transcriptase inhibitor, decreases in HIV-1 RNA of -1.4, -1.5 and -1.7 log_{10} copies/mL were observed on Day 10 at FTC doses of 25 mg, 100 mg, and 200 mg QD, respectively {Rousseau 2003}. These data suggest that the decrease in HIV-1 RNA of -1.03 log_{10} copies/mL observed with the 30 mg dose of GS-9131 evaluated in GS-US-180-0104 may not be providing the maximum reduction in viral load. This study will evaluate if greater viral load reduction may be observed at higher doses of GS-9131.

In Sentinel Cohort 1 Part 1, GS-9131 was administered once daily at doses of 60 mg for 10 days, in combination with the subject's current failing background regimen. GS-9131 60 mg represented a dose escalation (2-fold) over the previously evaluated 30 mg dose of GS-9131. Upon completion of the functional monotherapy, eligible participants discontinued the failing background regimen and initiated a complete regimen of GS-9131 (60 mg) in combination with BIC (30 mg) plus DRV (800 mg) + RTV (100 mg) for 24 weeks.

As only 2 of the 11 subjects achieved a 0.5 log decline in HIV-1 RNA during the functional monotherapy, the second Sentinel Cohort will evaluate 14 days of treatment with GS-9131 180 mg, representing a 3-fold dose escalation over the previously evaluated GS-9131 60 mg dose and a longer treatment period. GS-9131 exhibits approximately dose-proportional PK over the dose range of 10 mg to 60 mg {Begley 2018}. Assuming dose-proportional increases through 180 mg, projected exposures (AUC) at 180 mg of GS-9131 and GS-9148 in HIV-1 infected

subjects are 1797 (hr*ng/mL) and 2865 (hr*ng/mL), respectively (relative to HIV-infected subjects receiving 60 mg in Study GS-US-442-4148; Table 5). This dose range up to 180 mg allows sufficient dose separation to support evaluation of a dose/exposure-response relationship for GS-9131 in this study.

Safety data from Study GS-US-442-4148 demonstrated multiple daily doses of GS-9131 60 mg were well tolerated in HIV-infected subjects. Similarly, safety data from Study GS-US-180-4149 demonstrated multiple daily doses of GS-9131 60 mg, administered alone or in combination with DRV/COBI or TAF for up to 14 days, were well tolerated in healthy subjects. As no clinical safety data are currently available for GS-9131 180 mg, safety for these doses in female subjects are supported by safety margins in female animals in nonclinical toxicology studies. Safety margins relative to female animals in the nonclinical toxicology studies have been calculated for both GS-9131 and GS-9148 (Table 1). Safety, tolerability and PK of GS-9131 will be characterized in this study.

1.8.2. Bictegravir (BIC)

Preliminary data from Study GS-US-180-4149 demonstrate BIC (50 mg) exposures are ~90% higher following co-administration with DRV/COBI (800/150 mg) and GS-9131 , as compared to those observed in HIV-infected subjects receiving BIC/FTC/TAF (50/200/25 mg) in Phase 3 studies (Section 1.2.3.1). In an unboosted setting, BIC (75 mg) provides exposure modestly higher (~30%) than that observed in subjects receiving BIC/FTC/TAF (50/200/25 mg) (Study GS-US-141-1233). Based on these data, a 30 mg dose of BIC, when co-administered with DRV+RTV and GS-9131, and a 75 mg dose of BIC, when co-administered with TAF and GS-9131, are expected to provide BIC exposures similar to those observed following administration of BIC/FTC/TAF (50/200/25 mg), where it has been safe and efficacious in Phase 3 studies.

1.8.3. Ritonavir-Boosted Darunavir (DRV + RTV)

The dose of DRV (800 mg once daily) to be used in this study is the approved, recommended dose of DRV (boosted with RTV 100 mg) given once daily with food for the treatment of HIV-1 infection (Prezista United States Prescribing Information [USPI] and Norvir USPI). Ritonavir 100 mg is the approved, recommended dose of RTV as a PK enhancer.

1.8.4. Tenofovir Alafenamide (TAF)

The dose of TAF (25 mg once daily) to be used in this study is the approved, recommended dose in the fixed dose combinations (FDCs) Descovy (FTC/TAF), Odefsey (FTC/RPV/TAF), and Biktarvy (BIC/FTC/TAF) for the treatment of HIV-1 infection. Additionally, TAF (Vemlidy®) is approved for the treatment of chronic hepatitis B virus (HBV) infection.

1.9. Risk/Benefit Assessment for the Study

All patients with HIV-1 infection, including those with drug resistant viruses, benefit from receiving effective ART. The risks in the study patient population who are failing their current ARV regimen are considered to be low. Important risks will be appropriately managed by study inclusion/exclusion criteria, as well as close monitoring during the study.

All subjects will be monitored daily during the functional monotherapy period and at frequent intervals in Part 2 of the study. Monitoring will include clinical evaluation, safety laboratory tests, and HIV-1 RNA viral load. In addition, stopping criteria will be implemented on an individual and cohort basis and the study will be monitored by an independent data safety monitoring board as well as local ethics committees. Important risks will be appropriately managed by study inclusion/exclusion criteria, as well as close monitoring, including clinical evaluation, safety laboratory assessment, individual and by-cohort stopping rules, and HIV-1 RNA viral load monitoring during the study.

If a median of > 0.5 log decrease in HIV-1 RNA is observed following administration of GS-9131 180 mg in the second Sentinel Cohort, GS-9131 doses ≤ 180 mg may be evaluated in the Randomized Cohort.

The only significant effect identified in chronic animal studies with BIC was hepatobiliary toxicity in monkeys following 39 weeks of administration at a dose (1000 mg/kg/day) which produced plasma exposures to BIC that were 16-fold higher than those observed in patients at a 50 mg BIC dose. The effects were partially reversible after a 4- week period of non-exposure (recovery). No toxicity was observed at the mid-dose of BIC 200 mg/kg/day, which provided a margin of exposure 7-fold greater than the projected clinical exposure. Potential hepatobiliary toxicity is appropriately managed by study inclusion/exclusion criteria, close clinical and laboratory monitoring, as well as specific toxicity management guidance to investigators. As of 06 August 2018, 2740 subjects have been exposed to B/F/TAF in clinical trials with no evidence of hepatotoxicities. (Refer to BIC & TAF IB).

Consistent with other members of the INSTI class, BIC has been well-tolerated in clinical studies to date.

Tenofovir alafenamide (TAF) is a second generation oral prodrug of tenofovir (TFV), a nucleotide analog that inhibits HIV-1 reverse transcription. TAF is an approved medication and is marketed in multiple countries as FDC (Odefsey, Descovy, Genvoya, Biktarvy).

DRV and RTV are approved medications and are marketed in multiple countries under the tradenames Prezista and Norvir (Refer to the USPI). Use of DRV with RTV has been associated with abnormal liver function tests and hepatic toxicity and hypersensitivity reactions. The complete safety profiles for these drugs are available in their respective prescribing information. Parameters for discontinuation of the study drugs due to AEs are defined in this study protocol and will be closely followed.

Thus, the combination of GS-9131 with BIC and DRV + RTV or GS-9131 with BIC and TAF in TE individuals failing an NRTI/NNRTI containing regimen will provide an active regimen to the study cohorts. This active regimen will provide an important treatment option particularly in settings where routine drug resistance monitoring is not routinely available. The overall benefit-risk assessment of this study is favorable at this time.

1.10. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES

The primary objective of this study is:

- To evaluate the short-term antiviral potency of a regimen containing GS-9131 at doses up to 180 mg compared to placebo-to-match (PTM) GS-9131, each administered once daily with the existing failing ARV regimen, as demonstrated by the proportion of subjects with HIV-1 RNA decreases from baseline exceeding 0.5 $\log_{10}$ through 14 days of therapy in HIV-1 positive, ARV TE adult subjects with nucleos(t)ide resistant virus.

The secondary objectives of this study are:

Part 1

- To evaluate the efficacy of GS-9131 functional monotherapy as determined by the change from baseline in $\log_{10}$ HIV-1 RNA at Day 11 (Sentinel Cohort 1) or Day 15 (Sentinel Cohort 2 and Randomized Cohort)..

Part 2

- To evaluate the safety and efficacy of a regimen containing GS-9131 (60 mg) + bictegravir (BIC) + darunavir (DRV) + ritonavir (RTV) through 24 weeks of treatment in subjects from Sentinel Cohort 1 who switched from a failing regimen.

- To evaluate the safety and efficacy of a regimen containing GS-9131 + bictegravir (BIC) + tenofovir alafenamide (TAF) through 24 weeks of treatment in subjects from Sentinel Cohort 2 and Randomized Cohort who switched from a failing regimen.

- To characterize the pharmacokinetics (PK) of GS-9131 in treatment-experienced patients.

- To evaluate the number of subjects with treatment-emergent nucleos(t)ide reverse transcriptase inhibitor (NRTI), protease inhibitor (PI), and integrase strand-transfer inhibitor (INSTI) mutations at the time of virologic failure.

3. STUDY DESIGN

3.1. Endpoints

The primary endpoint of this study is:

- The proportion of subjects with plasma HIV-1 RNA decreases from baseline exceeding 0.5 $\log_{10}$ at Day 15 in the Randomized Cohort in Part 1.

The secondary endpoints of this study are:

Part 1

- The change from baseline in plasma $\log_{10}$ HIV-1 RNA (copies/mL) at Day 11 (Sentinel Cohort 1) and Day 15 (Sentinel Cohort 2 and Randomized Cohort) in Part 1.

Part 2

- The proportion of subjects with plasma HIV-1 RNA < 50 copies/mL as defined by the US FDA Snapshot algorithm at Week 24.
- The change from Part 2 baseline in plasma $\log_{10}$ HIV-1 RNA (copies/mL) at Week 24.
- The change from Part 2 baseline in CD4 cell count (cells/μL) at Week 24.
- Number of subjects with treatment-emergent NRTI, PI, and INSTI mutations at the time of virologic failure.

3.2. Study Design

This protocol describes a partially-randomized, partially-blinded, multicenter, two-part study. Part 1 consists of three cohorts: Two Sentinel Cohorts followed by a Randomized Cohort.

The Sentinel Cohort 1 is an open-label cohort that will enroll 10 HIV-1 positive subjects to receive GS-9131 60 mg plus their current failing regimen for 10 days. Subjects who achieve > 0.5 log decrease at Day 11 will initiate a regimen of GS-9131 (60 mg) + BIC (30 mg) + DRV (800 mg) + RTV (100 mg) for 24 weeks.

The Sentinel Cohort 2 is an open-label cohort that will enroll up to 10 HIV-1 positive subjects to receive GS-9131 180 mg plus their current failing regimen for 14 days. Subjects who achieve > 0.5 log decrease at Day 15 will proceed to Part 2 in which they will initiate a regimen of GS-9131 + BIC (75 mg) + TAF (25 mg) for 24 weeks.

The Randomized Cohort of the study is double-blinded, randomized, and will assess the efficacy of GS-9131 doses up to 180 mg versus placebo in up to 48 HIV-1 infected, TE subjects who are failing their current ARV regimen. Subjects who achieve > 0.5 log decrease at Day 15 will proceed to Part 2 in which they will initiate a regimen of GS-9131 + BIC (75 mg) + TAF (25 mg) for 24 weeks. Subjects who achieve > 0.5 log decrease at Day 15will proceed to Part 2 in which they will initiate a regimen of GS-9131 + BIC (75 mg) + TAF (25 mg) for 24 weeks.

3.3. Study Treatments

Subjects who provide written consent and meet all eligibility criteria will be allocated to one of the following treatment groups as follows:

Part 1: GS-9131 Functional Monotherapy

Part 1 consists of 3 cohorts:

Sentinel Cohort 1:

Approximately 10 TE viremic HIV-1 subjects will be enrolled to receive open-label GS-9131 60 mg in addition to their current failing ARV regimen.

Sentinel Cohort 2:

Up to 10 TE viremic HIV-1 subjects will be enrolled to receive open-label GS-9131 180 mg in addition to their current failing ARV regimen.

Randomized Cohort:

Up to 48 subjects failing their current ARV regimen will be randomized to GS-9131 (up to 180 mg) or PTM. These drugs will be added to their failing regimen for 14 days described below. Doses and number of cohorts will be determined by data from Sentinel Cohort 2:

- Treatment Arms A-C: GS-9131 up to 180 mg once daily + current failing ART regimen (n=12 per cohort)
- Treatment Arm D: PTM GS-9131 + current failing ART regimen (n=12)

Randomization will be stratified by HIV-1 RNA level (≤ 100,000 copies/mL and > 100,000 copies/mL) at screening.

Subjects enrolled in Part 1 who do not successfully complete the study drug doses in Part 1 will not continue onto Part 2 of the study.

Subjects enrolled in Part 1 who do not show a reduction in HIV RNA > 0.5 $\log_{10}$ from baseline to Part 2 Day 1 will have an Early Study Drug Discontinuation (ESDD) visit within 72 hours of laboratory results being available. They will have study medications discontinued and will not continue to Part 2.

Part 2 (Sentinel Cohort 1): GS-9131 + BIC + DRV+ RTV Regimen

In Part 2, subjects in Sentinel Cohort 1 will start a regimen consisting of GS-9131 (60 mg) + BIC (30 mg) + DRV+RTV (800 mg/100 mg) for 24 weeks. CCI [redacted]

Part 2: GS-9131 + BIC + TAF Regimen (Subjects in Sentinel Cohort 2 and Randomized Cohorts)

All subjects who successfully complete all study drug doses in Sentinel Cohort 2 and the Randomized Cohorts will discontinue study drug from Part 1 on Day 15. To continue to Part 2, subjects must have a > 0.5 $\log_{10}$ decline in plasma HIV-1 RNA from their pre-GS-9131 baseline in the 14 days of functional monotherapy. Since this result will not be immediately available at the completion of Part 1, all subjects completing Part 1 will continue on their failing regimen until results are available. Results will be available no later than 9 days after completion of Part 1. Subjects who meet criteria will proceed to Day 1 of Part 2. Any subjects in the Sentinel Cohort, and Treatment Arms A, B and C who do not meet the criterion for > 0.5 $\log_{10}$ decline in plasma HIV-1 RNA from their pre-GS-9131 baseline will not continue to Part 2. All subjects in Treatment Arm D will be eligible to continue to Part 2. In Part 2, subjects from the Sentinel Cohort 2 and the Randomized Cohort will start a regimen consisting of GS-9131 (up to 180 mg) + BIC (75 mg) + TAF (25 mg) as described below.

- Treatment Arms A-C: GS-9131 (up to 180 mg)+ BIC + TAF
- Sentinel Cohort 2 and Treatment Arm D: GS-9131 180 mg + BIC + TAF

At Week 8, subjects who have plasma HIV-1 RNA < 200 copies/mL or who have an HIV-1 RNA ≥ 200 copies/mL and a reduction in HIV-1 RNA > 1 $\log_{10}$ from baseline at any study visit will continue study medications.

Subjects who have a confirmed sub-optimal virologic response at Week 8 defined as plasma HIV-1 RNA ≥ 200 copies/mL and reduction in HIV-1 RNA ≤ 1 $\log_{10}$ from baseline at all study visits up to Week 12 may be discontinued from the study and further optimization of their ARV regimen if feasible will be done by the Investigator. Subjects meeting criteria for sub-optimal virologic response as further defined in Section 6.10.1 will be contacted for an ESDD visit and discontinued from the study within 72 hours of results being available.

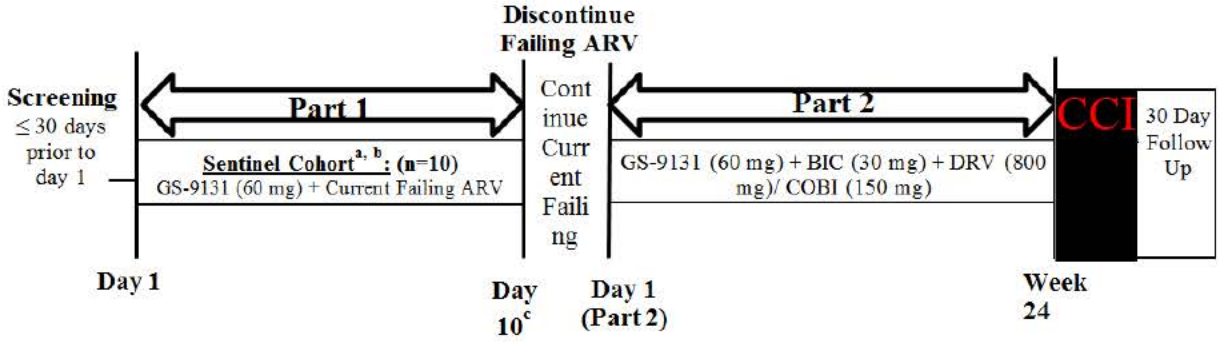
Subjects with protocol-defined virologic failure and evidence of treatment emergent resistance to any component of their regimen at any time will be discontinued from the study drug and treated with an ARV regimen chosen by the Investigator. For additional information, please reference ESDD (Section 6.4.1).

3.4. Duration of Treatment

The duration of the Sentinel Cohort 1 in Part 1 of the study is 10 days. Subjects who successfully complete the functional monotherapy, defined as a > 0.5 $\log_{10}$ reduction in plasma HIV-1 RNA from baseline, will be administered GS-9131 (60 mg) + BIC (30mg)+ DRV (800 mg) +RTV (100mg) through Week 24. CCI [redacted]

The duration of Sentinel Cohort 2 and Randomized Cohorts in Part 1 of the study is 15 days each. Subjects who successfully complete the 14 day functional monotherapy, defined as a > 0.5 log_{10} reduction in plasma HIV-1 RNA from baseline or who are from the PTM arm, will be administered GS-9131 + BIC (75 mg) + TAF (25 mg) through Week 24. Doses of GS-9131 for subjects in the Sentinel Cohort 2 and Placebo cohort will be 180 mg; doses of GS-9131 and PTM for subjects in the Randomized Cohorts Treatment Arms A-C will correspond to the respective dose selected for cohorts (A-C). All subjects will continue a regimen of GS-9131 + BIC (75 mg) + TAF (25 mg) at the assigned GS-9131 dose until determination of the optimal GS-9131 dose following Part 1 data review of the Randomized Cohort. CCI [redacted]

Figure 2. Study Schema – Cohort 1



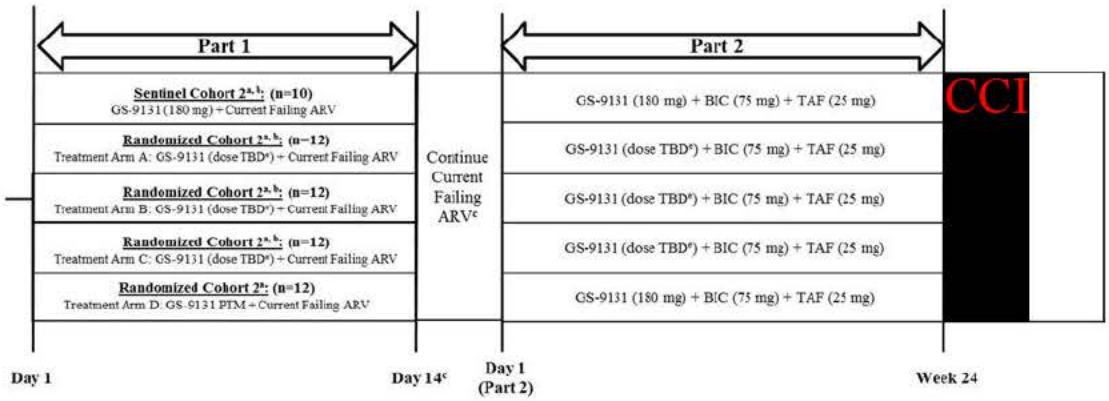
a Randomization and dosing into the Randomized Cohort of Part 1 will begin after the Day 10 safety and efficacy data from the 10 subjects in the Sentinel Cohort are reviewed.

b Subjects on GS-9131 (including all subjects in the Sentinel Cohort and those on Treatment Arm A, B, and C of the Randomized Cohort) who have a ≤ 0.5 log10 decline in HIV-1 RNA will be discontinued from the study and will not be eligible to continue into Part 2 of the study. The Sponsor will notify the site regarding subject enrollment criteria for Part 2 prior to the visit."

c Subjects who complete Day 10 of Part 1 (from either the Sentinel Cohort or Treatment Arm D of the Randomized Cohort) will discontinue their GS-9131 or PTM but remain on their failing ARV regimen until the site is notified of the subject's eligibility to proceed to Part 2.

CCI [redacted]

Figure 3. Study Schema – Cohort 2



a. Randomization and dosing into the Randomized Cohort of Part 1 will begin after the Day 15 safety and efficacy data from the Sentinel Cohort is reviewed.
b. Subjects on GS-9131 (including all subjects in the Sentinel Cohort and those on Treatment Arm A, B, and C of the Randomized Cohort) who have a $\leq$ 0.5 log10 decline in HIV-1 RNA will be discontinued from the study and will not be eligible to continue into Part 2 of the study. The Sponsor will notify the site regarding subject enrollment criteria for Part 2 prior to the visit.
c. Subjects who complete Day 14 of Part 1 (from either the Sentinel Cohort or Treatment Arm D of the Randomized Cohort) will discontinue their GS-9131 or PTM but remain on their failing ARV regimen until the site is notified of the subject's eligibility to proceed to Part 2.
d. [redacted]
e. In Part 1 Randomized Cohort 2, Treatment Arms A-C will be assigned up to three dose levels of GS-9131, up to 180 mg. The GS-9131 dose for Treatment Arm A-C will be determined following review of the Sentinel Cohort 2. Doses of GS-9131 for subjects in the randomized cohorts A-C will correspond to the respective dose selected in Part 2. All subjects will continue a regimen of GS-9131+BIC+TAF at the assigned GS-9131 until determination of the optimal GS-9131 dose following Part 1 data review of the randomized cohort.

CCI [redacted]

CCI [redacted]

[redacted]

CCI [redacted]

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Up to 68 subjects who meet eligibility criteria will be enrolled.

Replacement subjects may be enrolled for subjects who do not complete all procedures in the GS-913114-day functional monotherapy treatment for reasons other than discontinuation due to treatment related AEs.

4.2. Inclusion Criteria

Subjects must meet **all** of the following inclusion criteria to be eligible for participation in this study.

1) The ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study procedures

2) Non-pregnant/non-lactating females, ≥ 18 years of age at Screening

3) Plasma HIV-1 RNA ≥ 500 copies/mL at Screening Visit

4) Currently taking a failing ARV regimen that contains 2 NRTIs and an NNRTI

5) No prior or current ARV regimens containing integrase inhibitor (INSTI) or protease inhibitor (PI)

6) Screening genotype must show at least the following resistance mutation profile (a local genotype (within 3 months of the Screening visit) is acceptable for enrollment upon review by the Sponsor):

   a) K65R or at least 3 TAMS (defined as: M41L, D67N, K70R, L210W, T215F/Y or K219Q/E/N/R) or Q151M

   b) and at least one primary resistance mutation to an NNRTI (defined as L100I, K101E/P, K103N/R/S, V106M/A, V108I, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188C/H/L, G190A/E/Q/S, H221Y, P225H, F227C or M230L/I)

7) Adequate renal function:
   Estimated glomerular filtration rate ≥ 70 mL/min according to the Cockcroft-Gault formula for creatinine clearance {Cockcroft 1976}:

   - Female: $\frac{(140 - \text{age in years}) \times (\text{wt in kg})}{72 \times (\text{serum creatinine in mg/dL})} \times 0.85 = \text{CLcr (mL/min)}$

     $\frac{(140 - \text{age in years}) \times (\text{wt in kg})}{72 \times (\text{serum creatinine in } \mu\text{mol/L}) \times 0.6786} \times 0.85 = \text{CLcr (mL/sec)}$

8) Normal ECG (or if abnormal, determined by the Investigator to be not clinically significant)

9) CD4 > 100 cells/μL

10) Hepatic transaminases (AST and ALT) ≤ 2 × upper limit of normal (ULN)

11) Total bilirubin ≤ 1.5 mg/dL (≤ 26 μmol/L), or normal direct bilirubin

12) Adequate hematologic function (absolute neutrophil count ≥ 750/mm^3 (≥ 0.75 GI/L); platelets ≥ 50,000/mm^3 (≥ 50 GI/L); hemoglobin ≥ 10 g/dL (≥ 100g/L))

13) Serum amylase ≤ 2 × ULN (subjects with serum amylase > 2 × ULN will remain eligible if serum lipase is ≤ 2 × ULN)

14) A negative serum pregnancy test is required for female subjects of childbearing potential (as defined in Appendix 7). Female subjects of childbearing potential must agree to utilize protocol-recommended highly effective contraceptive methods or be non-heterosexually active or practice sexual abstinence (as defined in Appendix 7)

4.3. Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study.

1) An opportunistic illness indicative of stage 3 HIV diagnosed within the 30 days prior to screening (refer to Appendix 6)

2) Subjects with cirrhosis, compensated or decompensated (e.g., ascites, encephalopathy, or variceal bleeding)

3) Have been treated with immunosuppressant therapies or chemotherapeutic agents within 3 months of study screening, or expected to receive these agents or systemic steroids during the study (e.g., corticosteroids, immunoglobulins, and other immune- or cytokine-based therapies)

4) Current alcohol or substance use judged by the Investigator to potentially interfere with subject study compliance

5) Malignancy within 5 years of screening other than cutaneous Kaposi's sarcoma, completely resected non-melanoma skin cancer (basal cell carcinoma or non-invasive cutaneous squamous carcinoma), or completely resected carcinoma in-situ of the cervix (CIN 3) or anus (AIN 3). A prior malignancy treated with curative therapy and for which there has been no evidence of disease for at least five years prior to screening is allowed.

6) Active, serious infections (other than HIV-1 infection) requiring parenteral antibiotic or antifungal therapy within 30 days prior to Day 1

7) Participation in any other clinical trial, including observational studies, without prior approval from the sponsor is prohibited while participating in this trial

8) Use of an investigational drug other than GS-9131 or BIC or TAF

9) Any other clinical condition or prior therapy that, in the opinion of the Investigator, would make the subject unsuitable for the study or unable to comply with the dosing requirements

10) Known hypersensitivity to investigational medicinal products GS-9131, BIC, TAF, DRV, RTV, their metabolites, or formulation excipient

11) Acute hepatitis in the 30 days prior to randomization

12) Subjects with chronic hepatitis B virus infection are not permitted to participate.

- For the purposes of this study, chronic HBV infection is defined as: Positive HBV surface antigen and negative HBV surface antibody, regardless of HBV core antibody status

- Positive HBV core antibody and negative HBV surface antibody, regardless of HBV surface antigen status, at the screening visit

13) Subjects with chronic HCV infection requiring HCV therapy during the course of the study. Subjects with chronic HCV are eligible if the investigator does not anticipate treatment for HCV.

14) Active tuberculosis infection

15) Subjects receiving ongoing therapy with any of the medications listed in Section 5.4, including drugs not to be used with BIC, TAF, DRV and RTV.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding and Treatment Codes

It is the responsibility of the investigator to ensure that the subject is eligible for the study prior to enrollment. Subjects will be assigned a screening number at the time of consent.

Subjects who meet criteria will first be enrolled in the Sentinel Cohorts. The Sentinel Cohort 1 is an open-label cohort that will enroll 10 HIV-1 positive subjects to receive GS-9131 60 mg plus their current failing regimen for 10 days. The Sentinel Cohort 2 is an open-label cohort that will enroll up to 10 HIV-1 positive subjects to receive GS-9131 180 mg plus their current failing regimen for 14 days. Randomization and dosing of the Randomized Cohort of Part 1 will begin after the Day 15 safety, efficacy, and available PK data from the Sentinel Cohort 2 are reviewed.

Once eligibility has been confirmed for the Randomized Cohort and prior to or during the Part 1 Day 1 visit, the Investigator or designee will randomize the subject using the Interactive Web Response System (IWRS). Once a subject number has been assigned to a subject, it will not be reassigned to any other subject. The subject number assignment and randomization may be performed up to 3 days prior to the in-clinic Part 1 Day 1 visit provided that all screening procedures have been completed and subject eligibility has been confirmed. The Investigator must have results from genotype testing and confirmed eligibility before proceeding with subject randomization.

The IWRS will assign study drug bottle numbers of blinded GS-9131 or PTM at each study visit for each subject. At the beginning of Part 2, IWRS will assign GS-9131 + BIC + TAF.

5.1.1. Procedures for Breaking Treatment Codes

In the event of a medical emergency where breaking the blind is required to provide medical care to the subject, the investigator may obtain treatment assignment directly from the IXRS system for that subject. Gilead recommends but does not require that the investigator contact the Gilead medical monitor before breaking the blind. Treatment assignment should remain blinded unless that knowledge is necessary to determine emergency medical care for the subject. The rationale for unblinding must be clearly explained in source documentation and on the electronic case report form (eCRF), along with the date on which the treatment assignment was obtained. The investigator is requested to contact the Gilead medical monitor promptly in the event of any treatment unblinding.

Blinding of study treatment is critical to the integrity of this clinical trial and therefore, if a subject's treatment assignment is disclosed to the investigator, the subject will have study treatment discontinued. All subjects will be followed until study completion unless consent to do so is specifically withdrawn by the subject.

Gilead Pharmacovigilance and Epidemiology (PVE) may independently unblind cases for expedited reporting of suspected unexpected serious adverse reactions (SUSARs).

5.2. Description and Handling of Study Drug

5.2.1. Formulation

5.2.1.1. GS-9131 tablets, 30 mg

GS-9131 tablets, 30 mg, are round, film-coated white, plain-faced tablets. In addition to the active ingredient, the GS-9131 tablets contain the following inactive ingredients: lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, polyethylene glycol, talc and titanium dioxide.

5.2.1.2. Bictegravir tablets, 30 and 75 mg

Bictegravir tablets, 30 mg and 75 mg are round, film-coated yellow, plain-faced tablets. In addition to the active ingredient, the bictegravir tablets contain the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, crospovidone, sodium stearyl fumarate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide yellow.

5.2.1.3. Prezista® (DRV)

Information regarding the formulation of commercially available Prezista® (DRV) 800 mg tablets can be found in the package insert from the USPI or summary of product characteristics.

5.2.1.4. Norvir® (RTV)

Information regarding the formulation of commercially available Norvir® (RTV) 100 mg tablets can be found in the package insert from the USPI or summary of product characteristics.

5.2.1.5. Tenofovir alafenamide tablets (Vemlidy, TAF)

Tenofovir alafenamide (TAF) tablets are round, film-coated yellow tablets debossed with "25" on one side of the tablet and "GSI" on the other side. In addition to the active ingredient, the tablet cores contain lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide yellow.

5.2.1.6. Placebo-to-match GS-9131 tablets

Placebo-to-match (PTM) GS-9131 tablets 30 mg, are round, film-coated white, plain-faced tablets. The PTM GS-9131 tablets contain the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, polyethylene glycol, talc and titanium dioxide.

5.2.2. Packaging and Labeling

GS-9131 tablets, 30 mg, and PTM are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets, silica gel desiccant and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum-faced liner.

Bictegravir tablets, 30 mg and 75 mg, are packaged in white HDPE bottles. Each bottle contains 30 tablets, and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum-faced liner.

Tenofovir alafenamide (TAF) 25 mg tablets are packaged in white HDPE bottles. Each bottle contains 30 tablets, silica gel desiccant and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum-faced liner.

Commercially available Prezista and Norvir will be used for the study.

GS-9131, BIC, TAF, Prezista and Norvir to be distributed to centers in participating countries shall be labeled to meet applicable requirements of the US FDA, EU Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products [IMPs]), and/or other local regulations.

5.2.3. Storage and Handling

GS-9131, PTM GS-9131, BIC and TAF 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), or as otherwise specified on the label. Storage conditions are specified on the label. Until dispensed to the subjects, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure stability and proper identification, study drug(s) should not be stored in a container other than the container in which they were supplied. Keep the bottle tightly closed to protect from moisture.

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.

Commercial Prezista and Norvir will be used for the study. Further information regarding storage and handling are available in the Prescribing Information.

5.3. Dosage and Administration of GS-9131, BIC, DRV, RTV, TAF and PTM GS-9131

Study drug GS-9131, BIC, DRV, RTV, TAF, and PTM GS-9131 tablets will be provided by Gilead.

In Sentinel Cohort 1, subjects will begin assigned GS-9131 60 mg once daily. All other ARVs in the current regimen will be continued. All ARVs, including GS-9131, will be administered by directly observed therapy (DOT) on Days 1-10. If the current regimen includes ARVs taken more than once daily, taken at night, or with certain meals, additional doses will be documented

by the subject in a dosing diary provided for the study. GS-9131 must be administered by DOT on Days 1-10. Subjects who successfully complete all study drug doses through Day 10 and show a reduction in plasma HIV RNA > 0.5 $\log_{10}$ from their pre-GS-9131 baseline during functional monotherapy will discontinue their current failing regimen, and start an optimized regimen consisting of GS-9131 (60 mg) + BIC (30 mg) + DRV (800 mg) + RTV (100 mg) for 24 Weeks.

In Sentinel Cohort 2 and the Randomized Cohort, Part 1, subjects will begin assigned GS-9131 doses up to 180 mg, or PTM once daily. All other ARVs in the current regimen will be continued. All ARVs, including GS-9131, will be administered by directly observed therapy (DOT) on Days 1-14. If the current regimen includes ARVs taken more than once daily, taken at night, or with certain meals, additional doses will be documented by the subject in a dosing diary provided for the study. GS-9131 must be administered by DOT on Days 1-14.

Subjects in Sentinel Cohort 2 and Randomized Cohort Treatment Arms A-C who successfully complete all study drug doses in Part 1 and show a reduction in plasma HIV RNA > 0.5 $\log_{10}$ from their pre-GS-9131 baseline during functional monotherapy will enroll in Part 2, discontinue their current failing regimen, and start an optimized regimen consisting of GS-9131 (up to 180 mg) + BIC (75 mg) + TAF (25 mg). The GS-9131 dose in the combination regimen will be defined by the open-label or randomization dose given in Part 1. Reduction of plasma HIV RNA > 0.5 $\log_{10}$ from baseline must be demonstrated at Day 15. Dose of GS-9131 for the Randomized Cohort will be determined following review of Sentinel Cohort 2. The dose of GS-9131 for the OLE will be determined following review of the safety, efficacy and available PK data of the Randomized Cohort in Part 1 from Part 2.

Subjects will be instructed to bring all study medication in the original container to each clinic visit for drug accountability (unless otherwise specified in Section 5.5). The Investigator will be responsible for maintaining accurate records for all study drug bottles dispensed and tablets returned. The inventory and dispensing logs must be available for inspection by the study monitor. Study medication supplies, including partially used or empty bottles, must be accounted for by the study monitor prior to destruction or return.

5.4. Prior and Concomitant Medications For Subjects in Sentinel Cohort 2, Randomized Cohort and Part 2: GS-9131 + BIC + TAF

Invitro data suggest GS-9131 is a substrate of Pgp transporters and an inhibitor of OATP1B/1B3 transporters. Concomitant use of some medications and herbal/natural supplements with study drug may result in pharmacokinetic interactions resulting in increases or decreases in exposure of study drugs or these medications.

Representative medications listed in the following table and herbal/natural supplements are excluded or should be used with caution while subjects are participating in the study, this table is not exhaustive. During Part 1 of the study, physicians should also refer to the prescribing information for the current background regimen in addition to the recommendations listed in the table below. Subjects should discontinue disallowed concomitant medications 30 days prior to initiation of study drug.

In Part 2, the use of medications for the treatment of HIV, other than GS-9131 + BIC + TAF, are prohibited.

Table 6. Prior and Concomitant Medications*

Drug Class	Agents Disallowed**	Use Discouraged and To Be Used With Caution
Medications or oral supplements containing polyvalent cations (e.g., Mg, Al, Ca, Fe): Calcium or iron supplements Cation-containing antacids or laxatives Buffered medications		Administer Study Drug 2 hours before or 2 hours after taking medications or oral supplements containing polyvalent cations. Alternatively, Study Drug and medications or oral supplements containing polyvalent cations can be taken together with food.
Antiarrhythmic Agent	Dofetilide	
Anticonvulsants	Phenobarbital, Phenytoin, Carbamazepine, Oxcarbazepine	
Antimycobacterials	Rifampin, Rifapentine, Rifabutin	
Antiretrovirals	Any antiretroviral drug that is not part of the study regimen	
Statins		Pravastatin, pitavastatin, rosuvastatin, atorvastatin: Monitor for statin-related AEs
Herbal/Natural Supplements	St. John's Wort	

* For Prior and Concomitant Medications relevant to subjects in Part 2: DRV/r+BIC+GS-9131, see Appendix 8.
** Administration of any of the above medications must be discontinued at least 30 days prior to the Day 1 visit and for the duration of the study

Should subjects have a need to initiate treatment with any excluded concomitant medication, the Gilead Medical Monitor must be consulted prior to initiation of the new medication. In instances where an excluded medication is initiated prior to discussion with the Sponsor, the Investigator must notify Gilead as soon as he/she is aware of the use of the excluded medication.

5.5. Accountability of IMP

The investigator is responsible for ensuring adequate accountability of all used and unused IMP. This includes acknowledgement of receipt of each shipment of IMP (quantity and condition). All used and unused IMP dispensed to subjects must be returned to the site.

Study drug accountability records will be provided to each study site to:

- Record the date received and quantity of IMP kits
- Record the date, subject number, subject initials, and the IMP kit number dispensed
- Record the date, quantity of used and unused IMP kits returned, along with the initials of the person recording the information.

5.6. Investigational Medicinal Product Return or Disposal

Study drug return and disposal will be performed as outlined in Section 9.1.7.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Appendix 2 and Appendix 3 and described in the text that follows.

The investigator must document any deviation from protocol procedures and notify the sponsor or contact research organization (CRO).

6.1. Subject Enrollment and Treatment Assignment

It is the responsibility of the Investigator to ensure that subjects are eligible for the study prior to enrollment.

6.2. Pretreatment Assessments

6.2.1. Screening Visit

Subjects will be screened within 30 days before Part 1 Day 1 to determine eligibility for participation in the study. A single 14 day extension to the screening window may be granted with permission from the Medical Monitor. The following will be performed and documented at screening:

- Obtain written informed consent
- Obtain medical history, including history of HIV-1 disease-related events, complete ARV treatment history and all prior medications within 30 days of the Screening visit
- Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the Investigator)
- Height
- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature), including weight
- 12-lead ECG performed supine
- Obtain blood and urine samples as described in Sections 6.8.1, 6.8.2, Appendix 2, and Appendix 3.
- Review and document locally performed HIV resistance data including genotype and/or phenotype
  - HIV-1 genotype testing (integrase, protease, and reverse transcriptase) can be performed locally or centrally at the screening visit. Central lab HIV-1 genotype testing will not be performed for subjects that fail to meet other eligibility criteria.
- Review of AEs and concomitant medications

Subjects that meet all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 30 days after screening for the Day 1 Visit. Subjects must continue to take their prior treatment regimen until they are instructed to do otherwise. Subjects will be required to take their prior regimen through completion of Part 1 until the initiation of the Part 2 regimen.

From the time of obtaining informed consent through the first administration of IMP, all serious adverse events (SAEs), as well as any AEs related to protocol-mandated procedures, will be recorded on the AE eCRF. All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history, will be captured on the medical history eCRF. See Section 7 Adverse Events and Toxicity Management for additional details.

6.3. Treatment Assessments

6.3.1. Part 1 – Functional Monotherapy (Sentinel and Randomized Cohorts)

Subjects who meet criteria will first be enrolled in the Sentinel Cohort 1. The Sentinel Cohort 1 is an open-label cohort that will enroll approximately10 HIV-1 positive subjects to receive GS-9131 60 mg plus their current failing regimen for 10 days. The Sentinel Cohort 2 is an open-label cohort that will enroll approximately 10 HIV-1 positive subjects to receive GS-9131 180 mg plus their current failing regimen for 14 days.

Randomization and dosing into the Randomized Cohort of Part 1 will begin after review of the Day 15 safety and efficacy, and available PK data from the Sentinel Cohort 2.

Once eligibility has been confirmed for the Randomized Cohort and prior to or during the Part 1 Day 1 visit, the Investigator or designee will randomize the subject using the Interactive Web Response System (IWRS). Once a subject number has been assigned to a subject, it will not be reassigned to any other subject. The subject number assignment and randomization may be performed up to 3 days prior to the in-clinic Part 1 Day 1 visit provided that all screening procedures have been completed and subject eligibility has been confirmed. The Investigator must have results from genotype testing and confirm eligibility before proceeding with randomization.

- Review concomitant medications
- Record any SAEs and all AEs related to protocol mandated procedures occurring after signing of the consent form.
- Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the Investigator) **(Screening, Day 1, 14, and 15)**
- Symptom-directed physical examination **(Days 2, 7, 10, and 14)**
- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature), including weight **(Screening, Days 1, 3, 7, 10, and 14)**

- 12-lead ECG performed supine (approximately 1 hour post dose) **(Screening, Days 1, 10, and 15)**
- Obtain blood and urine samples as described in Sections 6.8.1, 6.8.2, Appendix 2, and Appendix 3.
- Collect subject dosing diary from all subjects (**Day 15**)
- Administration of study drug by DOT. Study drug, as well as other ARVs, will be administered by DOT once daily. Any additional doses of ARVs, other than GS-9131, that cannot be administered at the same time will be documented by the subject in a dosing diary provided for the study. Study drug should be administered at approximately the same time each day.

6.3.2. Part 2

All subjects must complete Part 1 prior to initiating any Part 2 Day 1 Visit procedures. Before proceeding into Part 2, subjects who have completed Day 14 of Part 1 will discontinue GS-9131 or PTM but remain on their failing regimen until the site is notified of the subject's eligibility to proceed to Part 2. This period shall be no longer than 14 days (for Sentinel Cohort 1)/9 days (Sentinel Cohort 2 and Randomized Cohort), while awaiting HIV-1 RNA results and the authorization to proceed from Gilead.

Once notified of their eligibility into Part 2 of the study, the subject will discontinue their failing regimen before initiating any Part 2 Day 1 study procedures. Subjects who received GS-9131 (including all subjects in the Sentinel Cohort 2 and those on Treatment Arms A-C of the Randomized Cohort) and had a ≤ 0.5 $\log_{10}$ decline in HIV-1 RNA will be discontinued from the study early and will have a 30 day visit following this visit.

In the event the plasma HIV-1 RNA test results performed by the central laboratory are delayed, a subject may still proceed to Part 2 of the study if the test results from the local laboratory show a reduction in plasma HIV-1 RNA > 0.5 $\log_{10}$ compared to pre-GS-9131 baseline during the 14 days of GS-9131 functional monotherapy in Part 1 of the study. If the local laboratory test results do not show a reduction in plasma HIV-1 RNA > 0.5 $\log_{10}$ and the central laboratory test results are not received ≤ 9 days from completion of Day 15 of Part 1, the subject will be discontinued from the study and will be required to return to the clinic 30 days after the last dose of study drug for the 30-Day Follow-Up Visit. After a subject has terminated their participation in the study, long-term care for the subject will remain the responsibility of their primary treating physician, who will have access to the subject's clinical information, including plasma HIV-1 RNA viral load and HIV-1 genotype testing results.

Part 2 Day 1 Treatment Assessments

All subjects who successfully complete all study drug doses in Part 1 and meet criteria to proceed to Part 2 will transition to Part 2and discontinue their current failing regimen.

The following evaluations are to be completed on Day 1 of Part 2. The Investigator must have confirmed eligibility before proceeding with the Part 2 Day 1 visit. The subject must complete all study procedures before being administered the study drug. Initiation of treatment with the study drug must take place within 24 hours after the Day 1 visit.

- Review concomitant medications
- Record any SAEs and all AEs related to protocol mandated procedures occurring after signing of the consent form
- Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the Investigator)
- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature), including weight
- Obtain blood and urine samples as described in Sections 6.8.1, 6.8.2, Appendix 2, and Appendix 3
- Document study drug dispensation and accountability for all study drugs dispensed
  - Subjects must be reminded to take study drug at the same time each day with food

6.3.3. Part 2 (Weeks 1-24)

All study visits are to be scheduled relative to the Part 2 Day 1 visit date. Visit windows are ± 4 days of the protocol-specified date through Week 24

The following will be performed at the Part 2 visits from Part 2 Week 1 up to Week 24:

- Review concomitant medications
- Record any SAEs and all AEs related to protocol mandated procedures occurring after signing of the consent form.
- Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the Investigator) **(Day 1, Weeks 12 and 24)**
- Symptom-directed physical examination **(Weeks 1, 2, 4, 8, and 18)**

- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature), including weight
- Obtain blood and urine samples as described in Sections 6.8.1, 6.8.2, Appendix 2, and Appendix 3
- Collect subject dosing diary from all subjects (**Weeks 4, 8, 12, 18, and 24)**
- Document study drug dispensation and accountability for all study drugs dispensed
  - Subjects must be reminded to take study drug at the same time each day with food
- Subjects who meet the criteria for virologic failure will be managed according to the Sub-optimal Virologic Response Section 6.10.2. and Management of Virologic Rebound Section 6.10.3

CCI [redacted]

6.4. Post-Treatment Assessments

6.4.1. Early Study Drug Discontinuation Visit for Premature Discontinuation from Study

Subjects who discontinue study drug before Week 24 will be required to complete an ESDD visit within 72 hours of stopping study drug. Prior to Week 24, if a subject discontinues study dosing (for example, as a result of an AE), every attempt should be made to keep the subject in the study and continue to perform the required study-related follow-up and procedures (see Section 6.5, Criteria for Discontinuation of Study Treatment). If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

CCI [redacted]

At the ESDD Visit, any evaluations showing abnormal results indicating that there is a possible or probable causal relationship with the study drug will be repeated weekly (or as often as deemed prudent by the Investigator) until the abnormality is resolved, returns to baseline (Day 1) value, or is otherwise explained.

The following evaluations are to be completed at the ESDD Visit:

- Review concomitant medications
- Record any SAEs and all AEs related to protocol mandated procedures occurring after signing of the consent form.
- Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the Investigator)
- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature), including weight
- Obtain blood and urine samples as described in Sections 6.8.1, 6.8.2, Appendix 2, and Appendix 3
- Collect subject dosing diary from all subjects
- Document study drug accountability for all study drug dispensed
- Document reason for discontinuation

6.4.2. 30 Day Follow-Up Visit

Subjects meeting criteria for sub-optimal virologic response in Part 1, defined as a reduction in plasma HIV RNA ≤ 0.5 $\log_{10}$ from pre-GS-9131 baseline after 10 days for Sentinel Cohort 1 and after 14 days for Sentinel Cohort 2 of GS-9131 functional monotherapy, will be required to return to the clinic 30 days after the last dose of study drug for the 30-Day Follow-Up Visit.

Subjects who complete the study drug through Week 24 CCI [redacted] will be required to return to the clinic 30 days after the last dose of study drug for the 30-Day Follow-Up Visit.

Subjects who prematurely discontinue study drug prior to Week 24 visit of the Part 2 phase and refuse to continue in the study will be asked to return to the clinic 30 days after the completion of the ESDD Visit for the 30-Day Follow-Up Visit.

Those subjects who prematurely discontinue study drug prior to the Week 24 visit of the Part 2 phase and continue in the study through at least one subsequent visit after the ESDD Visit <u>will not</u> be required to complete the 30-Day Follow-Up Visit.

CCI [redacted]

CCI [redacted]

For the purpose of scheduling a 30-Day Follow-Up Visit, a $\pm$ 6 days window may be used. The following evaluations are to be completed at the 30-Day Follow-Up Visit:

- Review concomitant medications
- Record any SAEs and all AEs related to protocol mandated procedures occurring after signing of the consent form.
- Symptom-directed physical examination
- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature), including weight
- Obtain blood and urine samples as described in Sections 6.8.1, 6.8.2, Appendix 2, and Appendix 3

At the 30-Day Follow-Up Visit, any evaluations showing abnormal results believed to be a reasonable possibility of a causal relationship with the study drugs will be repeated weekly (or as often as deemed prudent by the Investigator) until the abnormality is resolved, returns to baseline (Day 1) value, or is otherwise explained.

6.5. Criteria for Discontinuation of Study Treatment

Study medication will be discontinued in the following instances:

- Unacceptable toxicity, as defined by the toxicity management section of the protocol, 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 subject's best interest
- Subject request to discontinue for any reason
- Pregnancy during the study; refer to Appendix 7
- Development of active tuberculosis infection
- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC)

Study medication 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. Following resolution of intercurrent illness, the subject may resume study dosing at the discretion of the investigator.
- Lack of efficacy
- Subject noncompliance

6.5.1. Study Stopping Criteria

By Subject: Study drug dosing for a subject will be discontinued if that subject experiences a Grade 3 or Grade 4 treatment-emergent adverse event (AE) or confirmed laboratory abnormality judged by the study investigator to be possibly related to study drug, or any serious adverse event (SAE) considered to be possibly related to study drug.

By Sentinel Cohort: Study drug dosing during Part 1 for the Sentinel Cohorts will be discontinued if any of the following criteria is met:

- 2 or more subjects experiencing Grade 3 or Grade 4 treatment-emergent AEs judged by the study investigator to be possibly related to study drug, or
- 2 or more subjects experiencing confirmed Grade 3 or Grade 4 laboratory abnormalities, or
- 2 or more subjects experiencing any SAE that is considered to be possibly related to study drug.

For the Randomized Cohort and Part 2: If 2 or more subjects in Part 1 of the Randomized Cohort who are subsequently assigned to treatment cohorts in Part 2 experience a Grade 3 or 4 treatment emergent AE leading to study drug discontinuation or an SAE judged by the study investigator to be possibly related to study drug, the IDMC will be convened to review all preliminary safety data generated in subjects dosed to date.

Subjects will be followed as clinically indicated until the treatment-emergent AE or laboratory abnormality returns to baseline or is otherwise explained, whichever occurs first. Grade 3 and 4 laboratory abnormalities that are not confirmed by repeat testing will be managed according to the clinic's practice; a decision to reinitiate dosing may be made by Gilead in consultation with the investigator and after a safety review.

6.6. End of Study

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

6.7. Post Study Care

After a subject has completed/terminated their participation in the study, long-term care for the subject will remain the responsibility of their primary treating physician.

6.8. Clinical Laboratory Assessments

Blood and urine samples will be collected throughout the study as outlined below, within Section 6, in Appendix 2, and in Appendix 3.

6.8.1. Blood Samples

- **Blood samples will be collected for the following laboratory analyses** (Refer to Appendix 2, and Appendix 3)**:**

  — Serum pregnancy test (females of childbearing potential only). If the test is positive, the subject will not be enrolled **(Screening and Day 1 only).** Positive urine pregnancy tests will be confirmed with a serum test.

  — Follicle-stimulating hormone (FSH) (females who have ceased menstruating for greater than or equal to 12 months but do not have documentation of ovarian hormonal failure) Female subject post-menopausal for less than two year, if FSH < 40 mIU/ mL a serum pregnancy test will be required **(Screening only)**

  — Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CPK, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN)

  — Metabolic profile: Fasting (no food or drinks, except water, at least 8 hours prior to blood collection) glucose and lipid panel (total cholesterol, HDL, direct LDL, and triglycerides) collected at **Part 1 – Day 1, Part 2 – Day 1, Weeks 12** CCI [redacted].

    ■ If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to draw blood for the metabolic assessments

— eGFR according to the Cockcroft-Gault formula:

Female: $\frac{(140 - \text{age in years}) \times (\text{wt in kg})}{72 \times (\text{serum creatinine in mg/dL})} \times 0.85 = \text{CLcr (mL/min)}$

$\frac{(140 - \text{age in years}) \times (\text{wt in kg})}{72 \times (\text{serum creatinine in umol/L}) \times 0.6786} \times 0.85 = \text{CLcr (mL/sec)}$

— Hematology profile: complete blood count (CBC) with differential and platelet count.

— CD4 cell count and percentage

— Plasma HIV-1 RNA

— HBV blood panel: Hepatitis B virus surface antigen serology (HBsAg), Hepatitis B virus surface antibody (HBsAb) and Hepatitis B virus core antibody (HBcAb)

The following tests will be conducted by the central laboratory if the following criteria are met:

- If positive HBsAg, reflex testing for plasma HBV DNA, Hepatitis B virus e-antigen (HBeAg) (if negative, reflex Hepatitis B virus e-Antibody [HBeAb]), and quantitative HBsAg.
- If positive HBcAb with negative HBsAg and negative HBsAb: reflex testing for plasma HBV DNA (if positive, reflex HBeAg). If HBeAg is performed and found to be negative, reflex HBeAb

  If the subject meets the definition of HBV infection at screening, they will not be enrolled. If the subject meets the definition of HBV infection during the study, HBV treatment and study continuation must be discussed with the Gilead Medical Monitor.

— Hepatitis C Virus (HCVAb) serology. Subjects who are HCVAb positive will have a HCV RNA test performed.

CCI [redacted]

— Plasma, CCI [redacted] and serum storage sample for safety, or virology testing

— HIV-1 genotype/phenotype testing for subjects with virologic failure **(Screening, Days 1 15 (Sentinel Cohort 2)**

— Sparse PK Samples:

- Single Anytime PK Sample: collected without regard to time of dosing **(Part 2 - Weeks 2, 8 and 24)**
- Timed PK Sample: collected at predose and one within 15 minutes-4 hours post dose **(Part 2 - Weeks 4, 12, and 18)**

— Intensive PK

- Plasma samples will be collected on **Day 10** for Sentinel Cohort 1 and **Day 14** for Sentinel Cohort 2 and Randomized Cohort.
- Prior to the administration of study drug, a predose (< 5 minutes prior to dosing) will be collected. Subjects will then take an observed dose of study drug at the clinic. Additional blood samples will be collected at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 24 hour post dose.

— PBMC samples will be collected on **Day 10 for Sentinel Cohort 1 and Day 14 for Sentinel Cohort 2 and Randomized Cohort:** Predose (<5 minutes prior to dosing), 1, 2, 6 and 24 hours post dose

CCI [redacted]

— Subjects must be instructed to not to take their study drugs on the morning of their visit. Prior to the administration of study drug, a predose (< 5 minutes prior to dosing) plasma blood sample will be collected. Subjects will then take an observed dose of study drug at the clinic. Additional plasma blood samples will be collected at 0.5, 1, 1.5, 2, 3, 4, 6, and 8 hours post dose. PBMC PK samples will be collected at predose (<5 minutes prior to dosing), 1, 2, and 6 hours post dose.

CCI [redacted]

6.8.2. Urine Samples

- **Urine samples will be collected for the following laboratory analyses** (Refer to Appendix 2 and Appendix 3):

— Urinalysis

— Urine pregnancy testing (females of childbearing potential only)

CCI [redacted]

CCI [redacted]

CCI [redacted]

6.10. Virologic Failure

Virologic failure is defined as virologic rebound (Section 6.10.2) or as suboptimal virologic response in relation to pre-GS-9131 baseline plasma HIV-1 RNA levels at the time points described below.

6.10.1. Suboptimal Virologic Response

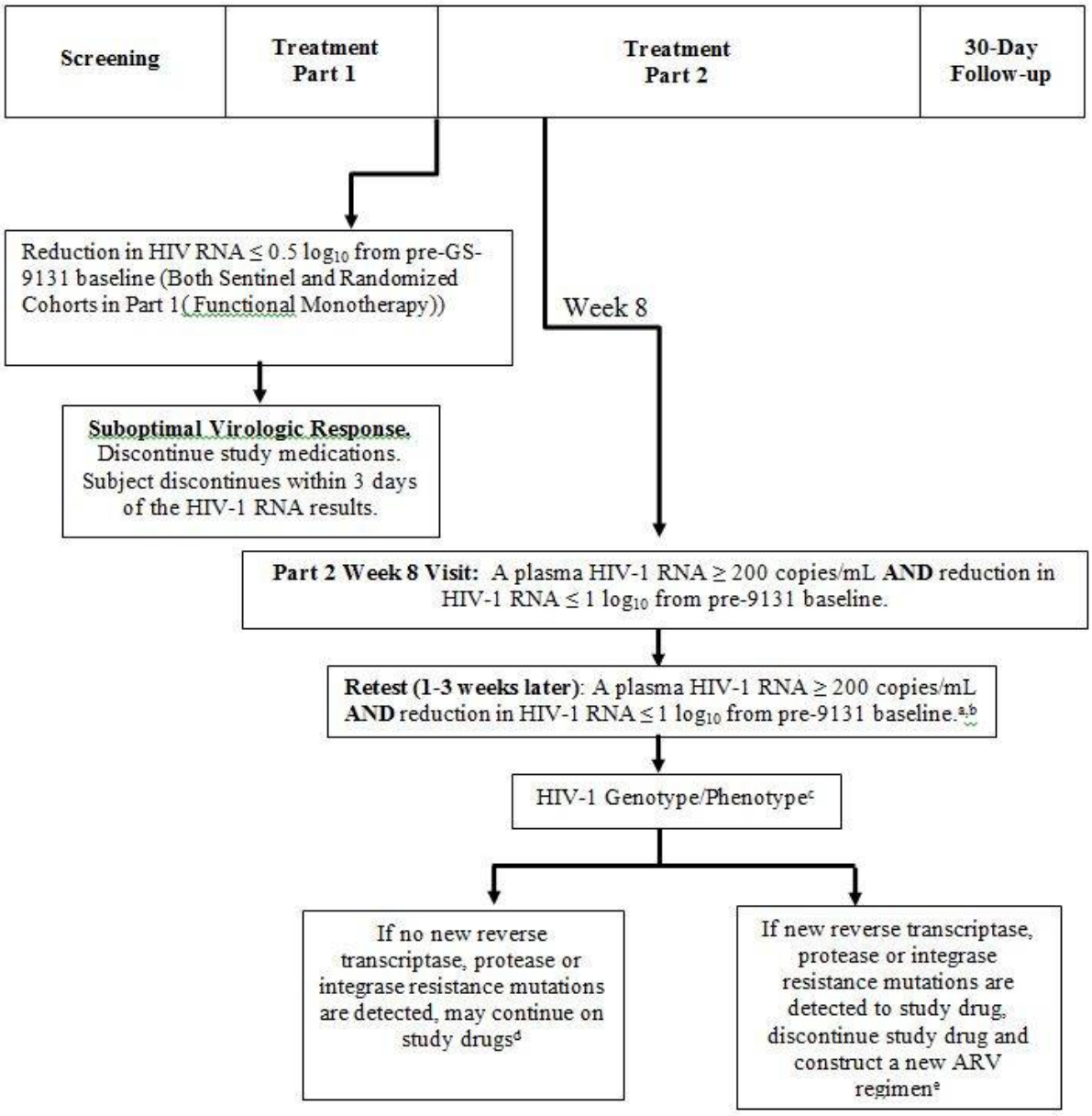
Subjects who meet the criteria listed below will be considered to have suboptimal virologic response (Figure 4):

A) Functional monotherapy Sentinel Cohort 1: Suboptimal virologic response for Sentinel Cohort 1 is defined as a reduction in plasma HIV RNA ≤ 0.5 $\log_{10}$ from pre-GS-9131 baseline after 10 days of GS-9131 functional monotherapy. This is assessed at Day 11 in Sentinel Cohort 1. Subjects meeting criteria for suboptimal virologic response will be contacted for an ESDD visit and discontinued from the study within 72 hours of these results being available.

Functional monotherapy Sentinel Cohort 2 and Randomized Cohorts: Suboptimal virologic response is defined as a reduction in plasma HIV RNA ≤ 0.5 $\log_{10}$ from pre-GS-9131 at Day 15 during GS-9131 functional monotherapy period (excludes placebo group). Subjects meeting criteria for suboptimal virologic response will be contacted for an ESDD visit and discontinued from the study within 72 hours of these results being available.

B) All Subjects Part 2: Suboptimal virologic response is defined as plasma HIV-1 RNA ≥ 200 copies/mL AND reduction in HIV-1 RNA ≤ 1 $\log_{10}$ from pre-GS-9131 baseline at the Week 8 visit with confirmation at the next scheduled or unscheduled visit. Subjects with suboptimal virologic response at Week 8 will have a repeat test of plasma HIV-1 RNA 1-3 weeks later. If the repeat test shows a suboptimal virologic response defined as plasma HIV-1 RNA ≥ 200 copies/mL AND reduction in HIV-1 RNA ≤ 1 $\log_{10}$ from pre-GS-9131 baseline, an HIV-1 genotype/phenotype will be done. If no new resistance to study drugs is detected from the genotype or phenotype, the subject may remain on study drugs and a repeat test of HIV-1 RNA should be conducted (1 to 3 weeks after the last HIV-1 RNA test). Investigators should carefully evaluate the benefits and risks of remaining on study drug for each individual subject and document this assessment in the on-site medical record. If new resistance to study drugs is detected, subjects will discontinue study drugs. For subjects who are off study drug but remain on study, it will be the Investigator's discretion to optimize their regimen and manage virologic rebound.

Figure 4. Suboptimal Virologic Response Schema



a If virologic rebound is not confirmed, the subject will remain on their current regimen.
b If virologic rebound is confirmed and the HIV-1 RNA is ≥ 200 copies/mL, the HIV-1 genotype/phenotype (reverse transcriptase, protease, and integrase) will be analyzed.
c Based on the results of the genotypic/ phenotypic assays, the subject will remain on study drugs or study drugs will be discontinued. If genotyping/ phenotyping assay fails, a new ARV regimen may be configured at the discretion of the Investigator.
d If no new resistance is detected, HIV-1 RNA will be repeated (1-3 weeks later). Investigator reviews study drug continuation/discontinuation options and discusses with the Medical Monitor prior to study drug discontinuation
e A new ARV regimen may be configured, at the Investigator's discretion, and the subject will remain in the study.

6.10.2. Virologic Rebound

Subjects who meet the criteria listed below will be considered to have virologic rebound:

A) At any visit, after achieving HIV-1 RNA < 50 copies/mL, a rebound in HIV-1 RNA ≥ 50 copies/mL, which is subsequently confirmed at the following scheduled or unscheduled visit;

   OR

B) At any visit, a > 1 $\log_{10}$ increase in HIV-1 RNA from the nadir which is subsequently confirmed at the following scheduled or unscheduled visit

6.10.3. Management of Virologic Rebound

Following the unconfirmed virologic rebound, subjects will be asked to return to the clinic for a scheduled or unscheduled blood draw (1 to 3 weeks after the date of the original test that resulted in HIV-1 RNA virologic rebound) for confirmation of virologic rebound. If virologic rebound is confirmed at the scheduled or unscheduled visit and the HIV-1 RNA is ≥ 200 copies/mL, the blood sample from the confirmation visit will be the primary sample used for HIV-1 genotypic and phenotypic testing. After a subject's first post-baseline resistance test, additional testing will be conducted on a case-by-case basis. Any subject may be discontinued at Investigator's discretion or per local treatment guidelines.

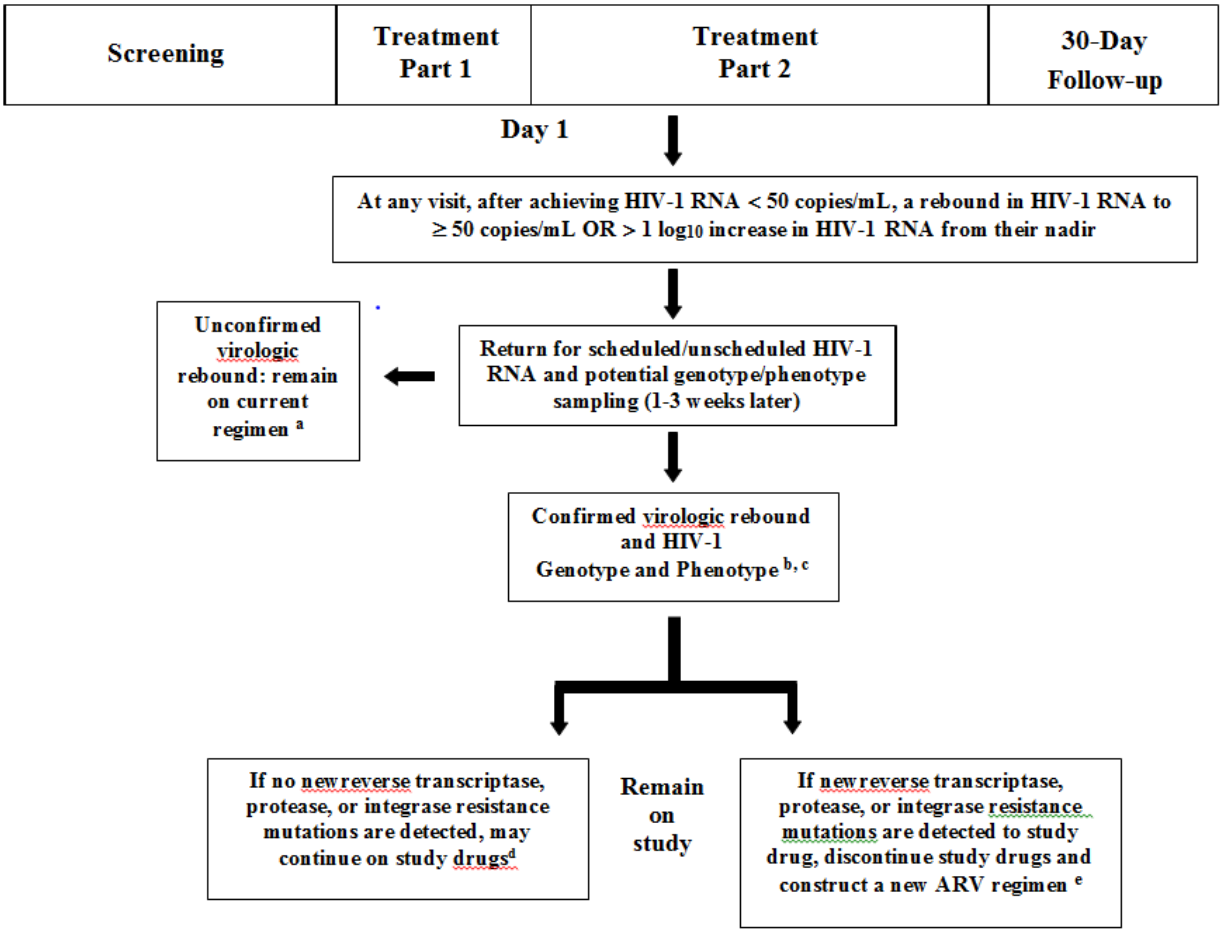
If no new resistance is detected from the genotype or phenotype, the subject may remain on study drugs and a repeat HIV-1 RNA should be conducted (1 to 3 weeks after date of test with HIV-1 RNA ≥ 50 copies/mL). Investigators should carefully evaluate the benefits and risks of remaining on study drug for each individual subject and document this assessment in the on-site medical record.

Subjects who are noncompliant on an ongoing basis will be considered for discontinuation per the Investigator's discretion or local treatment guidelines. Investigators who opt to discontinue study drugs for an individual subject must discuss with the Medical Monitor prior to study drug discontinuation.

For subjects who are off study drug but remain on study, it will be the Investigator's discretion to manage virologic rebound.

Please refer to Figure 5 for the management of subjects who meet the criteria for virologic rebound.

Figure 5. Virologic Rebound Schema



a If virologic rebound is not confirmed, the subject will remain on their current regimen.
b If virologic rebound is confirmed and the HIV-1 RNA is ≥ 200 copies/mL, the HIV-1 genotype/phenotype (reverse transcriptase, protease and integrase) will be analyzed.
c Based on the results of the genotypic/ phenotypic assays, the subject will remain on study drugs or study drugs will be discontinued. If genotyping/ phenotyping assay fails, a new ARV regimen may be configured at the discretion of the Investigator.
d If no new resistance is detected, HIV-1 RNA will be repeated (1-3 weeks later). Investigator reviews study drug continuation/discontinuation options and discusses with the Medical Monitor prior to study drug discontinuation
e A new ARV regimen may be configured, at the Investigator's discretion, and the subject will remain in the study.

6.10.4. Subjects with HIV-1 RNA ≥ 50 copies/mL at Study Discontinuation and Week 24

Subjects with HIV-1 RNA ≥ 50 copies/mL at study discontinuation or last visit will be considered virologic failures. Subjects with HIV-1 RNA ≥ 50 copies/mL at Week 24 will be asked to return for an unscheduled visit within the visit window for a retest.

Subjects with HIV-1 RNA ≥ 200 copies/mL at study drug discontinuation, last visit, or at Week 24 will also have resistance testing conducted.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal product, which 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 medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or post-treatment complications that occur as a result of protocol-specified procedures, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

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 adverse event 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 (e.g., hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.7.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be preexisting and should be documented on the medical history eCRF.

7.1.2. Serious Adverse Events

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

- Death
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject 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.)
- In-patient 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 subject or may require intervention to prevent one 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. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

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 to IMP therapy using clinical judgment and the following considerations:

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

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 (e.g., 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, (e.g., venipuncture)

7.2.2. Assessment of Severity

AE severity should be recorded and graded according to the GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 5). For adverse events 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.

The distinction between the seriousness and the severity of an adverse event should be noted. Severe is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events.

7.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Gilead

Requirements for Collection Prior to Study Drug Initiation:

After informed consent, but prior to initiation of study medication, the following types of events should be reported on the eCRF: all SAEs and AEs related to protocol-mandated procedures.

7.3.1. Adverse Events

Following initiation of study medication, all AEs, regardless of cause or relationship, until 30-days after last administration of study IMP must be reported to the eCRF database as instructed.

All AEs 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.

7.3.2. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occur after the subject first consents to participate in the study (i.e., signing the informed consent) and throughout the duration of the study, including the protocol-required post treatment follow-up period, must be reported to the eCRF database and Gilead PVE as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Any SAEs and deaths that occur after the post treatment follow-up visit but within 30 days of the last dose of study IMP, regardless of causality, should also be reported. Investigators are not obligated to actively seek SAEs after the protocol-defined follow up period; however, if the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of IMP, he/she should promptly document and report the event to Gilead PVE

- All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline.

Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead PVE within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.

- If for any reason it is not possible to record the SAE information electronically, i.e., the eCRF database is not functioning, record the SAE on the paper serious adverse event reporting form and submit within 24 hours to:

Gilead PVE contact information:

Fax: PPD

E-mail:PPD

- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines.

- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject 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 in the concomitant medication section of the subject's eCRF and the event description section of the SAE form.

7.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States 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 IMP. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

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

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (e.g., clinical chemistry, hematology, and urinalysis) independent of the underlying medical condition that require medical or surgical intervention or lead to investigational medicinal product interruption or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., 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. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (i.e., anemia) not the laboratory result (i.e., decreased hemoglobin).

Severity should be recorded and graded according to the GSI Toxicity Grading Scale which can be found in Appendix 5).

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.

7.6. Toxicity Management

All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in Appendix 4 and as outlined below.

Refer to Section 6.5 for additional specific discontinuation criteria. Specific toxicity discontinuation criteria in Section 6.5 and Appendix 4 supersede the general toxicity guidelines below, and in general, where a discrepancy is present, the more conservative criteria apply. The Gilead Medical Monitor should be consulted prior to study drug discontinuation when medically feasible.

7.6.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

Continue study drug at the discretion of the investigator.

7.6.2. Grades 3 Laboratory Abnormality or Clinical Event

- All Grade 3 and 4 laboratory abnormalities should be repeated immediately to confirm toxicity grade. Confirmation of toxicity grade is required prior to the next dose of investigational medicinal product for any Grade 3 and 4 laboratory abnormality that in the opinion of the Investigator is clinically significant and may pose a risk to the subject's safety.
- For a Grade 3 clinically significant laboratory abnormality or clinical event, IMP may be continued if the event is considered to be unrelated to IMP.

- For a Grade 3 clinical event, or clinically significant laboratory abnormality confirmed by repeat testing, that is considered to be related to IMP, IMP should be withheld until the toxicity returns to ≤ Grade 2.
- If a laboratory abnormality recurs to ≥ Grade 3 following re-challenge with IMP and is considered related to IMP, then IMP should be permanently discontinued and the subject managed according to local practice. Recurrence of laboratory abnormalities considered unrelated to IMP may not require permanent discontinuation.

7.6.3. Grade 4 Laboratory Abnormality or Clinical Event

For a Grade 4 clinical event or clinically significant Grade 4 laboratory abnormality confirmed by repeat testing that is considered related to IMP, IMP should be permanently discontinued and the subject managed according to local practice. The subject 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.

Investigational medicinal product may be continued without dose interruption for a clinically non-significant Grade 4 laboratory abnormality (e.g., Grade 4 creatine kinase [CK] after strenuous exercise or triglyceride elevation that is nonfasting or that can be medically managed) or a clinical event considered unrelated to IMP.

Treatment-emergent toxicities will be noted by the investigator and brought to the attention of the Gilead Medical Monitor, who will have a discussion with the investigator and decide the appropriate course of action. Whether considered treatment-related or not, all subjects 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.

7.7. Special Situations Reports

7.7.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of adverse events associated with product complaints, occupational exposure with an AE, pregnancy reports regardless of an associated AE, and AE in an infant following exposure from breastfeeding.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.

Misuse is defined as any intentional and inappropriate use of a medicinal product 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 medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Product complaint is defined as a complaint arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

Occupational exposure is defined as exposure to a medicinal product as a result of one's professional or non-professional occupation.

7.7.2. Instructions for Reporting Special Situations

7.7.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study medication and throughout the study, including the post study drug follow-up period, to Gilead PVE using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

Refer to Section 7.3 and the eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

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

Any premature termination of pregnancy (e.g., a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. 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 7.3. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead PVE.

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

Email: PPD and Fax: PPD

Refer to Appendix 7 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.7.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to Gilead PVE within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study IMP and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

Special situations involving non-Gilead concomitant medications do not need to be reported on the special situations report 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.

Refer to Section 7.3 and the eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

All clinical sequelae in relation to these special situation reports 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.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective of the study is to evaluate the short-term antiviral potency of GS-9131 functional monotherapy compared to PTM GS-9131, each administered once daily with the existing failing ARV regimen, as demonstrated by the proportion of subjects achieving HIV-1 RNA > 0.5 $\log_{10}$ decreases from baseline after up to 14 days of therapy in HIV-1 positive, ARV TE adult subjects with nucleos(t)ide resistant virus.

The secondary objectives of this study are:

Part 1

- To evaluate the efficacy of GS-9131 functional monotherapy as determined by the change from baseline in $\log_{10}$ HIV-1 RNA at Day 11 for Sentinel Cohort 1 and Day 15 for Sentinel Cohort 2 and Randomized Cohort.

Part 2

- To evaluate the safety and efficacy of a regimen containing GS-9131 (60 mg) + BIC + DRV + RTV through 24 weeks of treatment in subjects from Sentinel Cohort 1 who switched from a failing regimen as determined by achievement of HIV-1 RNA < 50 copies/mL at Week 24.
- To evaluate the safety and efficacy of a regimen containing GS-9131(up to 180 mg) + BIC + TAF through 24 weeks of treatment in Subjects from Sentinel Cohort 2 and Randomized Cohort who switched from a failing regimen as determined by achievement of HIV-1 RNA < 50 copies/mL at Week 24.
- To characterize the PK of GS-9131 following multiple doses of GS-9131 in TE patients.
- To evaluate the number of subjects with treatment-emergent NRTI, PI, and INSTI mutations at the time of virologic failure.

8.1.2. Primary Endpoint

The primary endpoint is the proportion of subjects with plasma HIV-1 RNA decreases from baseline exceeding 0.5 $\log_{10}$ at Day 15 in the Randomized Cohort in Part 1.

8.1.3. Secondary Endpoints

The secondary endpoints include:

- The change from baseline in plasma $\log_{10}$ HIV-1 RNA (copies/mL) at Day 11 for Sentinel Cohort 1 and Day 15 for Sentinel Cohort 2 and Randomized Cohort in Part 1.
- Number of subjects with treatment-emergent NRTI, PR, and INSTI mutations at the time of virologic failure.

8.1.4. Other Endpoints of Interest

- The proportion of subjects with plasma HIV-1 RNA < 50 copies/mL as defined by the US FDA Snapshot algorithm at Week 24 in Part 2.
- The change from Part 2 baseline in plasma $\log_{10}$ HIV-1 RNA (copies/mL) at Week 24 in Part 2.
- The change from Part 2 baseline in CD4 cell count (cells/μL) at Week 24 in Part 2.

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. All Enrolled Analysis Set

The all enrolled analysis set includes all subjects who enroll into the study either in the sentinel cohorts or randomized cohort. This is the primary analysis set for by-subject listings.

8.2.1.2. Efficacy

The primary analysis set for efficacy analysis is defined as follows:

8.2.1.2.1. Full Analysis Set (FAS)

Two full analysis sets will be defined, one for the Randomized Cohort in Part 1 and one for Part 2. The FAS for the Randomized Cohort in Part 1 will include all subjects who (1) are randomized to Part 1 Randomized Cohort, and (2) have received at least one dose of study medication in Part 1. Subjects in the Randomized Cohort in Part 1 will be grouped according to the treatment to which they were randomized. The FAS for Part 2 will include all subjects who (1) are enrolled into Part 2, and (2) have received at least one dose of study medication in Part 2.

8.2.1.2.2. Per-Protocol (PP) Analysis Set

The Per-Protocol analysis set will only be defined for the Randomized Cohort in Part 1. The Per-Protocol analysis set will include all subjects who (1) are randomized to Part 1 Randomized Cohort, (2) have received at least one dose of study medication in Part 1, and (3) have not committed any major protocol violation in the randomized cohort in Part 1, including the violation of key entry criteria. Subjects in the PP analysis set will be grouped according to the treatment they actually received.

8.2.1.3. Safety

Two safety analysis sets will be defined, one for the Randomized Cohort in Part 1 and one for Part 2. The safety analysis set for the Randomized Cohort in Part 1 will include all subjects who (1) are randomized to Part 1 Randomized Cohort, and (2) received at least one dose of study drug in Part 1. Subjects in the safety analysis set in Part 1 will be grouped according to the treatment they actually received. The safety analysis set for Part 2 will include all subjects enrolled into Part 2 who have received at least one dose of study drug in Part 2. All the data collected up to 30 days after subjects permanently discontinue their study regimen will be included in the safety summaries.

8.2.1.4. Pharmacokinetics

8.2.1.4.1. Pharmacokinetic Analysis Set for Part 1

8.2.1.4.2. The PK analysis set will include all subjects who (1) are enrolled or randomized into the study, (2) have received at least one dose of study medication and (3) have at least 1 non-missing PK concentration data for any analyte of interest. The PK analysis set will be used for analyses of general pharmacokinetics.Pharmacokinetic Analysis Set for Part 2

8.2.1.4.3. The PK analysis set will include all subjects who (1) are enrolled or randomized into the study, (2) have received at least one dose of study medication and (3) have at least 1 non-missing PK concentration data for any analyte of interest. The PK analysis set will be used for analyses of general pharmacokinetics**.** PBMC PK Analysis Set

The PBMC PK analysis set will include all subjects who (1) are enrolled or randomized into the study, (2) have received at least one dose of study medication and (3) have at least 1 non-missing PBMC PK concentration data for any analyte of interest. The PBMC analysis set will be used for analyses of general pharmacokinetics.

8.2.1.5. Sentinel Cohort Analysis Set

The Sentinel Cohort analysis set will include all subjects who are enrolled into the Sentinel Cohorts and received at least 1 dose of study medication. Both safety and efficacy data will be analyzed using this analysis set for subjects enrolled in Part 1 Sentinel Cohorts.

8.3. Data Handling Conventions

HIV-1 RNA results of "No HIV-1 RNA detected" and "< 20 cp/mL HIV-1 RNA Detected" will be imputed as 19 copies/mL for analysis purposes.

Natural logarithmic transformation of plasma concentrations and PK parameters will be applied for PK analysis.

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 plus or minus one significant digit, respectively (e.g., if the result of a continuous laboratory test is < 20, a value of 19 will be assigned).

Missing data can have an impact upon the interpretation of the trial data. In general, values for missing data will not be imputed. However, a missing pre-treatment laboratory result would be treated as normal (i.e., no toxicity grade) for the laboratory abnormality summary.

All available data for subjects that do not complete the study will be included in data listings.

8.4. Demographic Data and Baseline Characteristics

Demographic and baseline characteristics will be summarized for each part and cohort (Part 1) using standard descriptive methods including sample size, mean, SD, median, Q1, Q3, minimum, and maximum for continuous variables and frequency and percentages for categorical variables.

Demographic data will include race, ethnicity, and age.

Baseline characteristics will include body weight, height, body mass index, and eGFR, HIV-1 infection, and enrollment distribution by randomization stratum (if applicable) will be summarized.

For the Randomized Cohort in Part 1, the Cochran–Mantel–Haenszel (CMH) test will be used to compare treatment arms for categorical demographic and baseline characteristics, and the Wilcoxon rank sum test will be used for continuous demographic and baseline characteristics. No comparison is needed for the Sentinel Cohorts in Part 1 and Part 2.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The primary efficacy endpoint is the proportion of subjects with HIV-1 RNA decreases from baseline exceeding 0.5 $\log_{10}$ copies/mL at Day 15 for Part 1, Randomized Cohort. Subjects who have missing HIV-1 RNA values at Day 15 will be considered as without an HIV-1 RNA decrease from baseline exceeding 0.5 $\log_{10}$ copies/mL at Day 15. The difference between each of the GS-9131 treatment groups and the placebo group will be compared using a Fisher's exact test at a two-sided significant level of 0.05.

The null hypothesis is that there is no difference in proportion of subjects with HIV-1 RNA decreases exceeding 0.5 $\log_{10}$ at Day 15 between each of the GS-9131 treatment groups and the placebo group; the alternative hypothesis is that there is a difference in the proportion of subjects with HIV-1 RNA decreases exceeding 0.5 $\log_{10}$ copies/mL at Day 15 between each of the GS-9131 treatment groups and the placebo group.

The primary analysis of the efficacy will be based on FAS in Part 1.

8.5.2. Secondary Analyses

For Part 1 Randomized Cohort, the change from baseline in plasma $\log_{10}$ HIV-1 RNA (copies/mL) and CD4 cell count at Day15 will be summarized and compared between each of GS-9131 groups and placebo group using a two-sided Wilcoxon rank sum test at a two-sided significant level of 0.05.

For Part 1 Sentinel Cohorts, the proportion of subjects with HIV-1 RNA decreases from baseline exceeding 0.5 $\log_{10}$ copies/mL at Days 11 (Sentinel Cohort 1) and 15 (Sentinel Cohort 2) and the change from baseline in plasma log10 HIV-1 RNA (copies/mL) and CD4 cell count at Days 11 (Sentinel Cohort 1) and 15 (Sentinel Cohort 2) will be summarized using the Sentinel Cohort analysis set.

For Part 2, the percentage of subjects with plasma HIV-1 RNA < 50 copies/mL at Week 24, as defined by the FDA snapshot algorithm and missing = failure/excluded methods, will be summarized and the 95% confidence intervals using the Clopper-Pearson Exact method will also be presented. The change from Part 2 baseline in log10 HIV-1 RNA, CD4 cell count and percentage at Week 24 will be summarized using descriptive statistics. These analyses will be based on the FAS in Part 2. As a sensitivity analysis these analyses will be repeated by utilizing subjects from randomized cohort only.

8.6. Safety Analysis

All safety analyses will be performed using the safety analysis set by part and cohort.

For each part and cohort, all safety data collected on or after the date that the study drug was first administered up to the date of the last dose of study drug plus 30 days, unless specified otherwise, will be summarized for subjects in the safety analysis set according to the study drug received.

Data for the pretreatment period and the period after the date of last dose of study drug plus 30 days will be included in data listings for all enrolled subjects.

The safety analysis set for the Sentinel Cohorts is the Sentinel Cohort analysis set.

8.6.1. Extent of Exposure

A subject's extent of exposure to study drug will be generated from the study drug administration page in CRF. Exposure data will be summarized by part, cohort, and treatment.

Duration of exposure to study drug will be expressed as the number of days for Part 1 and weeks for Part 2 between the first and last dose of the study drug, inclusive, regardless of temporary interruptions in study drug administration and summarized by treatment in each part and cohort.

Dosing information for individual subjects will be listed.

8.6.2. Adverse Events

Clinical and laboratory AEs will be coded using the MedDRA. System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT) will be attached to the clinical database.

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent AE will be defined as any AE with onset date on or after the study drug start date and no later than 30 days after the study drug stop date; or any AE leading to study drug discontinuation.

Summaries (number and percentage of subjects) of treatment-emergent AEs (by SOC, HLT [if applicable], and PT) will be provided by part, cohort, and treatment. Additional summaries will include summaries for AEs by grade, Investigator's assessment of relationship to study drug, and effect on study drug dosing.

AEs will be reviewed on an ongoing basis for events that might meet the definition of Category C events that are indicative of an AIDS-Defining Diagnoses. If further information is needed to assess whether the event meets the Category C definition, a Clinical Endpoint Summary Sheet will be sent to the Investigator to collect additional pertinent information and the Gilead Medical Monitor will review the possible Category C events and approve the events that meet the definition. Those events that do meet the Category C definition of an AIDS-Defining Diagnosis will be summarized. A listing of Category C, AIDS-Defining Diagnosis can be found in Appendix 6.

8.6.3. Laboratory Evaluations

Selected laboratory data will be summarized using only observed data. Absolute values and changes from baseline at all scheduled visits will be summarized.

Graded laboratory abnormalities will be defined using the grading scheme defined in Grading of laboratory abnormalities provided in Appendix 5.

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline at any time post baseline up to and including the date of last dose of study regimen plus 30 days, will be summarized by part, cohort, and treatment. If baseline data are missing, then any graded abnormality (i.e., at least a Grade 1) will be considered treatment-emergent. The maximum toxicity grade will be summarized by laboratory parameter.

Laboratory abnormalities that occur before the first dose of study regimen or after the subject has been discontinued from treatment plus 30 days will be included in a data listing.

8.6.4. Other Safety Evaluations

Vital signs and safety ECG data will be summarized as appropriate.

8.7. Pharmacokinetic Analysis

For the plasma PK, the concentration data of any analyte of interest (eg, GS-9131, BIC, or other available analytes, as appropriate) will be summarized by nominal sampling time using descriptive statistics for each part. Pharmacokinetic parameters will be listed and summarized using descriptive statistics by part. Plasma concentrations over time from intensive PK will be plotted in semi-logarithmic and linear formats as mean ± standard deviation, and median (Q1, Q3). Additional analyses may be conducted.

For the sparse PK in Part 2, the pharmacokinetics of GS-9131, BIC, and TAF may be summarized in a listing,

For subjects who have evaluable concentrations in PBMCs, the PK concentration and parameters of GS-9148-DP or TFV-DP will be listed and summarized using descriptive statistics.

8.8. Biomarker Analysis

Not Applicable.

8.9. Sample Size

For the Randomized Cohort in Part 1, a total of 48 HIV-1 positive adults, randomized in a 1:1:1:1 ratio to 4 arms (3 dose levels of GS-9131 up to 180 mg, and placebo) achieves 85% power to detect a 61.7% difference in the proportion of subjects with HIV-1 RNA decreases from baseline exceeding 0.5 $\log_{10}$ between at least one of the GS-9131 treatment arms and placebo arm at Day 21. For sample size and power computation, it is assumed that 70% of subjects in each GS-9131 arm achieved a reduction exceeding 0.5 $\log_{10}$ HIV-1 RNA while 8.3% of subjects in the placebo arm achieved such a reduction (based on internal Viread Study 907), and a Fisher's exact test at a two-sided significance level of 0.05 was conducted.

Sample size and power calculations were made using nQuery Advisor 6.0.

8.10. Data Monitoring Committee

An external Independent Data Monitoring Committee (IDMC) will review the progress, efficacy, and safety data of this study while the study is ongoing. The committee will convene after approximately 50% of subjects enrolled in Part 2 complete Week 12 of the study. However, Gilead will defer to the IDMC for any decision to convene earlier or more frequently. The IDMC will examine the safety results of the trial and also focus on logistical issues such as accrual, retention, quality of clinical and laboratory data, and implications of results of external studies. Blinding will be preserved for Part 1 during the conduct of the study and access to unblinded data will be limited to designated parties.

No formal stopping rules will be used by the IDMC for safety outcomes. Rather, a clinical assessment will be made to determine if the nature, frequency, and severity of adverse events associated with a study regimen warrant the early termination of the study in the best interest of the participants.

An analysis for the Week 12 IDMC meeting will be conducted after approximately 50% of subjects enrolled in Part 2 complete Week 12 of the study.

Gilead does not have a prior intent to ask the IDMC to consider early termination of the study even if there is early evidence of favorable efficacy.

8.11. Analysis Schedule

The Part 1 analysis will be conducted after all subjects either complete their Part 1 last scheduled visit or prematurely discontinue from the study drug before the last scheduled visit in Part 1. The Week 24 analysis will be conducted after all subjects complete Week 24 or prematurely discontinue from the study. Final analysis will be conducted after all subjects complete the study.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. These standards are consistent with the European Union Clinical Trials Directive 2001/20/EC and GCP Directive 2005/28/EC.

The investigator will ensure adherence to the basic principles of GCP, as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR 50, and 21 CFR 56.

The investigator and all applicable subinvestigators will comply with 21 CFR 54, providing documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug under study. 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 subject completes the protocol-defined activities.

9.1.2. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Review and Approval

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to the local regulatory agency and/or ethics committee. The investigator will not begin any study subject activities until approval from all applicable bodies has been received and has been documented and provided as a letter to the investigator.

Before implementation, the investigator (or sponsor as appropriate according to local regulations) will submit to and receive documented approval from the local regulatory agency and/or ethics committee any modifications made to the protocol or any accompanying material to be provided to the subject after initial approval, with the exception of those necessary to reduce immediate risk to study subjects.

9.1.3. 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 and before undertaking any study-related procedures. The investigator must use the most current approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by local requirements. The consent form will inform subjects about pharmacogenomic testing and sample retention, if applicable as per protocol.

9.1.4. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, another unique identifier (as allowed by local law), and an identification code will be recorded on any form or biological sample submitted to the Sponsor or laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions. NOTE: The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial. Subject 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, eCRF, the IMP, 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 study site to any third party or otherwise into the public domain.

9.1.5. 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 two categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, CRF and query forms, ethics committee and governmental approval with correspondence, informed consent, 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 subject:

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria, i.e, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);

- Documentation of the reason(s) a consented subject 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 date (including dose regimen) of IMP, including dates of dispensing and return;
- Record of all AEs and other safety parameters (start and end date, and including causality and severity);
- Concomitant medication (including start and end date, dose if relevant; dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

All clinical study documents must be retained by the investigator until 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, United States, 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, until 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 subject, appropriate copies should be made for storage away from the site.

9.1.6. Case Report Forms

For each subject consented, an eCRF casebook will be completed by an authorized study staff member whose training for this function is completed in EDC. The eCRF casebook will only capture the data required per the protocol schedule of events and procedures. The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only after all data related to eligibility have been received. Subsequent to data entry, a study monitor will perform

source data verification within the EDC system. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site 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 (e.g., data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to any interim time points or database lock (as instructed by Gilead), the investigator will use his/her log in credentials 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 trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Investigational Medicinal Product Accountability and Return

Gilead recommends that used and unused IMP supplies be returned to the shipping facility from which it came for eventual destruction. The study monitor will provide instructions for return. If return is not possible, the study monitor will evaluate each study center's IMP disposal procedures and provide appropriate instruction for destruction of unused IMP supplies. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead QA, the site may destroy used (empty or partially empty) and unused IMP supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files.

If IMP is destroyed on site, the investigator must maintain accurate records for all IMP destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the IMP. Upon study completion, copies of the IMP accountability records must be filed at the site. Another copy will be returned to Gilead.

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

9.1.8. Inspections

The investigator will make available all source documents and other records for this trial to Gilead's appointed study monitors, to ethics committees, 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 subjects, may be made only by Gilead. The investigator (or the sponsor, as appropriate according to local regulations) must submit all protocol modifications to the regulatory agency and ethics committee, and any other bodies as required in accordance with local legislation and receive all documented approvals before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency(ies). 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.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years, and

- The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.

No such communication, presentation, or publication will include Gilead's confidential information (see Section 9.1.4).

The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

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, e.g., 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 trial payments, meal, 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 in order to verify the accuracy of the data recorded in the eCRF.

The monitor is responsible for routine review of the eCRF 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 monitor should have access to any subject records needed to verify the entries on the eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of 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 medical 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

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

10. REFERENCES

Barditch-Crovo P, Deeks SG, Collier A, Safrin S, Coakley DF, Miller M, et al. Phase I/II trial of the pharmacokinetics, safety, and antiretroviral activity of tenofovir disoproxil fumarate in HIV-1 infected adults. Antimicrob Agents Chemother 2001;45 (10):2733-9.

Begley R, Majeed SR, Cao H, West SK, vu A. Pharmacokinetics, Food Effect, and Safety of GS-9131, a Novel N(t)RTI for Use in Treatment of Experienced HIV-Infected Patients. ASCPT 2018 Annual Meeting; 2018 21-24 March; Orlando, FL.

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.

Department of Health and Human Services (DHHS). Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Developed by the HHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC). Revised 12 February 2013. Available at: http://aidsinfo.nih.gov/guidelines. Accessed: 2013 February 12. 2013.

Genvoya, Gilead Science Inc. GENVOYA® (elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide) tablets, for oral use. US Prescribing Information. Foster City, CA. Revised: August. 2018:

Lundgren JD, Clumeck N, Rockstroh J, Ryom L. European AIDS Clinical Society (EACS) Guidelines. Version 7.0 October. 2013:

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Developed by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC) Available at: http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Last Updated 14 July. 2016.

PREZCOBIX, Janssen Ortho LLC. PREZCOBIX (darunavir and cobicistat) tablets, for oral use. US Prescribing Information. Titusville, NJ. Revised: June. 2018:

Rousseau FS, Wakeford C, Mommeja-Marin H, Mxoham C, Harris J, Hulett L, et al. Prospective randomized trial of emtricitabine versus lamivudine short-term monotherapy in human immunodeficiency virus-infected patients. J Infect Dis 2003;188 (11):1652-8.

Ruane PJ, Dejesus E, Berger D, Markowitz M, Bredeek UF, Callebaut C, et al. Antiviral Activity, Safety, and Pharmacokinetics/Pharmacodynamics of Tenofovir Alafenamide as 10-Day Monotherapy in HIV-1-Positive Adults. J Acquir Immune Defic Syndr 2013;63 (4):449-55.

Schneider E, Whitmore S, Glynn KM, Dominguez K, Mitsch A, McKenna MT. Revised surveillance case definitions for HIV infection among adults, adolescents, and children aged <18 months and for HIV infection and AIDS among children aged 18 months to <13 years--United States, 2008. MMWR Recomm Rep 2008;57 (RR-10):1-12.

Squires K, Pozniak AL, Pierone G, Jr, Steinhart CR, Berger D, Bellos NC, et al. Tenofovir disoproxil fumarate in nucleoside-resistant HIV-1 infection. Ann Intern Med 2003;139 (5, Part 1):313-21.

TenoRes Study Group. Global epidemiology of drug resistance after failure of WHO recommended first-line regimens for adult HIV-1 infection: a multicentre retrospective cohort study. Lancet Infect Dis 2016;16:565-75.

Thompson MA, Aberg JA, Cahn P, Montaner JS, Rizzardini G, Telenti A, et al. Antiretroviral treatment of adult HIV infection: 2010 recommendations of the International AIDS Society-USA panel. JAMA 2010;304 (3):321-33.

UNAIDS. Fact Sheet 2016: Global Statistics-2015. Available at: http://www.unaids.org/en/resources/documents/2016/UNAIDS_FactSheet. 2016.

Williams I, Churchill D, Anderson J, Boffito M, Bower M, Cairns G, et al. British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2012 (Updated November 2013. All changed text is cast in yellow highlight.). HIV Med 2014;15 Suppl 1:1-85.

World Health Organization (WHO). Consolidation Guidelines on HIV Prevention, Diagnosis, Treatment and Care for Key Populations. 2016.

11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404

STUDY ACKNOWLEDGEMENT

A Phase 2 Study to Evaluate the Efficacy of GS-9131 Functional Monotherapy in HIV-1-Infected Adults Failing a Nucleos(t)ide Reverse Transcriptase Inhibitor-Containing Regimen with Nucleos(t)ide Reverse Transcriptase Inhibitor Resistant Virus

GS-US-442-4148 Amendment 3, 01 November 2018

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

PPD

Name (Printed)
Author

PPD

01 NOV 2018
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 _____

Appendix 2. Study Procedures Table – Cohort 1

Study Procedures	Screening[a,b]	Part 1 (Sentinel Cohort 1 Randomized)[c] Days											Part 2 Weeks[e,j] (+/- 4 days)								CCI		
		1	2	3	4	5	6	7	8	9	10	11[d]	Day 1	1	2	4	8	12	18	24	Every 12 Weeks	30 Day Follow-up[c]	ESDD[h]
Informed Consent	X																						
Medical History	X																						
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	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	X	X[i]	X
Complete Physical Exam	X	X										X	X					X		X			X
Symptom-Directed Physical Exam			X					X						X	X	X	X		X		X	X[i]	
12-Lead ECG (performed supine)	X	X										X	X							X		X	
Height	X																						
Vital Signs and Weight	X	X						X				X	X	X	X	X	X	X	X	X	X	X	X
Hematology Profile	X	X						X				X	X	X	X	X	X	X	X	X	X	X[i]	X
Chemistry Profile	X	X						X				X	X	X	X	X	X	X	X	X	X	X[i]	X
Urinalysis	X	X						X				X	X			X		X		X	X	X[i]	X
Metabolic Profile[k]		X											X					X[k]		X[k]	X		
Estimated Glomerular Filtration Rate	X											X	X	X	X	X	X	X	X	X	X	X[i]	X
Serum Pregnancy Test[l]	X	X																					
Urine Pregnancy Test[l]	X	X										X	X			X	X	X	X	X	X	X	X
FSH Testing[v]	X																						
Plasma, Serum, CCI Storage Sample		X										X	X			X	X	X	X	X	X	X	X
HCV Serology[m]	X																			X			
HBV blood panel	X												X							X	X		

Study Procedures	Screening[a,b]	Part 1 (Sentinel Cohort 1 Randomized)[c] Days											Part 2 Weeks[e,j] (+/- 4 days)								CCI		ESDD[h]
		1	2	3	4	5	6	7	8	9	10	11[d]	Day 1	1	2	4	8	12	18	24	Every 12 Weeks	30 Day Follow-up[c]	
Plasma HIV-1 RNA	X	X	X	X				X			X	X	X	X	X	X	X	X	X	X	X	X	X
CD4 Cell Count	X	X										X	X	X	X	X	X	X	X	X	X	X	X
HIV-1 Genotype/ Phenotype[j]	X	X										X											X
Timed PK Sample[n]																X		X	X				
Single Anytime PK Sample[o]															X		X			X			
CCI																							
Intensive PK Sampling[p]											X					X[f]	X[f]						
PBMC Sampling[r]											X												
Randomization[s]		X																					
Collect Subject Dosing Diary to Subjects												X				X	X	X	X	X	X		X
In-clinic Dosing[t]		X	X	X	X	X	X	X	X	X	X												
Study Drug Dispensation[u]													X	X	X	X	X	X	X	X	X		
Drug Accountability													X	X	X	X	X	X	X	X	X		X

a Evaluations to be completed within 30 days prior to Part 1 Day 1 visit. A single 14 day extension to the screening window may be granted with permission form the Medical Monitor

b Results from the screening genotype report and confirmed eligibility must be obtained before proceeding with Day 1 Visit. Local genotype at the Screening Visit is acceptable for enrollment upon review by the Sponsor. A single 14 day extension to the screening window may be granted with permission form the Medical Monitor if the genotype results are delayed.

c Randomization and dosing into the Randomized Cohort of Part 1 will begin after the Day 10 safety, efficacy and available PK data from the 10 subjects in the Sentinel Cohort are reviewed.

d Before proceeding into Part 2, subjects who have completed Day 10 of Part 1 (from either the Sentinel or Randomized Cohorts) will discontinue GS-9131 or PTM but remain on their failing regimen until the site is notified of the subject's eligibility to proceed to Part 2**.** This period shall be no longer than 14 days while awaiting Day 10 HIV-1 RNA results and the authorization to proceed from Gilead. Once notified of their eligibility into Part 2 of the study, the subject will discontinue their failing regimen before initiating any Part 2 Day 1 study procedures. In the event the plasma HIV-1 RNA test results performed by the central laboratory are delayed beyond 14 days, a subject may still proceed to Part 2 of the study if the test results from the local laboratory show a reduction in plasma HIV-1 RNA > 0.5 $\log_{10}$ compared to pre-GS-9131 baseline after 10 days of GS-9131 functional monotherapy in Part 1 of the study.

e All study visits are to be scheduled relative to the Part 2 Day 1 visit date. Visit windows are ± 4 days of the protocol specified date through Week 8, ± 4 days of the protocol specified date through Week 24. CCI

[redacted]

h ESDD visit to occur within 72 hours of last dose of study drug. Subjects will be asked to continue attending the scheduled study visits through the Week 24 visit even as the subject discontinues study drug.

i Any AE or test showing abnormal results that is believed to have a possible or probable causal relationship with the study drug will be repeated weekly (or as often as deemed prudent by the Investigator) until the abnormality is resolved, returns to baseline (Day 1) value, or is otherwise explained.

j HIV-1 genotype/phenotype testing for subjects with confirmed virologic failure and HIV-1 RNA >200 copies/mL, at early study discontinuation or Week 24. Following virologic rebound, subjects will be asked to return to the clinic (1-3 weeks later) prior to the next scheduled visit or at the next scheduled study visit for a HIV-1 RNA and HIV-1 genotype/phenotype (reverse transcriptase, protease, and integrase) blood draw. Based on the results of this testing, subjects should be managed according to the Virologic Rebound Schema (Section 6.10).

k Collected fasted (no food or drinks, except water, at least 8 hours prior to blood collection) only at Part 2 – Day 1, Week 12, and Week 24. Collected non-fasted at all other visits. If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to draw blood for the assessments.

l Females of childbearing potential only. Urine and serum pregnancy test will be done at Screening and Day 1. If the urine and serum test is positive at screening, the subject will not be enrolled. A positive urine pregnancy test at any visit will be confirmed with a serum test. If the test is positive the subject will be discontinued from the study. .

m Hepatitis C Virus (HCFAb) serology. Subjects who are HCVAb positive will have a HCV RNA test performed.

n Timed PK Sample: collected at predose and one within 15 minutes-4 hours post dose **(Part 2 – Weeks 4, 12 and 18)**

o Single Anytime PK Sample: collected without regard to time of dosing **(Part 2 – Weeks 2, 8 and 24)**

p Intensive PK samples will be collected on Part 1 – Day 10**.** Prior to the administration of study drug, a predose (<5 minutes prior to dosing) blood sample will be collected. **Subjects will then take an observed dose of study drug at the clinic.** Additional blood samples will be collected at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 24 hour post dose.

[redacted]

r PBMC collection on Day 10: Predose (<5 minutes prior to dosing), 1, 2, 6 and 24 hours post dose.

s Randomization may be performed up to 3 days prior to the in-clinic Day 1 visit provided that all screening procedures have been completed, and subject eligibility has been confirmed.

t All study medication in Part 1 will be delivered by directly observed therapy on Days 1-10.

u Subjects must be reminded to take study drug at the same time each day except on days with Timed PK sample and Intensive PK.

v For female subject post-menopausal for less than two years, if FSH <40 mIU/ mL a serum pregnancy test will be required

Appendix 3. Study Procedures Table – Sentinel Cohort 2/Randomized Cohort Part 1

		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Informed Consent	X															
Medical History	X															
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Exam	X	X														X
Symptom-Directed Physical Exam			X					X			X				X	
12-Lead ECG (performed supine)	X	X														X
Height	X															
Vital Signs and Weight	X	X		X				X			X				X	
Hematology Profile	X	X		X		X		X			X				X	X
Chemistry Profile	X	X		X		X		X			X				X	X
Urinalysis	X	X		X		X		X			X				X	X
Metabolic Profile[k]		X														
Estimated Glomerular Filtration Rate	X	X		X		X			X			X			X	
Serum Pregnancy Test[l]	X	X														
Urine Pregnancy Test[l]	X	X									X				X	
FSH Testing[v]	X															
Plasma, Serum, CCI Storage Sample		X		X		X		X			X	X			X	X
HCV Serology[m]	X															
HBV blood panel	X															
Plasma HIV-1 RNA	X	X		X				X			X				X	X
CD4+ Cell Count	X	X									X				X	X
HIV-1 Genotype/ Phenotype[j]	X	X									X					X
Whole blood sample for genotypic testing		X														

		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
CCI																
Intensive PK Sampling[p]															X	
PBMC Sampling[r]															X	
Randomization[s]		X														
Collect Subject Dosing Diary to Subjects																X
In-clinic Dosing[t]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study Procedures	Part 2 Weeks[e,j] (+/- 4 days)								CCI	30 Day Follow-up[f]	ESDD[h]
	Day1	1	2	4	8	12	18	24	Every 12 Weeks		
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X[i]	X
Complete Physical Exam	X					X		X			X
Symptom-Directed Physical Exam		X	X	X	X		X		X	X[i]	
12-Lead ECG (performed supine)	X							X		X	
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X	X
Hematology Profile	X	X	X	X	X	X	X	X	X	X[i]	X
Chemistry Profile	X	X	X	X	X	X	X	X	X	X[i]	X
Urinalysis	X			X		X		X	X	X[i]	X
Metabolic Profile[k]	X					X[k]		X[k]	X		
Estimated Glomerular Filtration Rate	X	X	X	X	X	X	X	X	X	X[i]	X
Serum Pregnancy Test[l]											
Urine Pregnancy Test[l]	X			X	X	X	X	X	X	X	X
Plasma, Serum, CCI Storage Sample	X			X	X	X	X	X	X	X	X
HCV Serology[m]								X			

	Part 2 Weeks[e,j] (+/- 4 days)								CCI	30 Day Follow-up[CCI]	ESDD[h]
Study Procedures	**Day1**	**1**	**2**	**4**	**8**	**12**	**18**	**24**	**Every 12 Weeks**		
HBV blood panel	X							X	X		
Plasma HIV-1 RNA	X	X	X	X	X	X	X	X	X	X	X
CD4+ Cell Count	X	X	X	X	X	X	X	X	X	X	X
HIV-1 Genotype/ Phenotype[j]											X
Timed PK Sample[n]				X		X	X				
Single Anytime PK Sample[o]			X		X			X			
Intensive PK Sampling[p]				X[CCI]	X[CCI]						
Collect Subject Dosing Diary to Subjects				X	X	X	X	X	X		X
Study Drug Dispensation[u]	X	X	X	X	X	X	X	X	X		
Drug Accountability	X	X	X	X	X	X	X	X	X		X

a Evaluations to be completed within 30 days prior to Part 1 Day 1 visit. A single 14 day extension to the screening window may be granted with permission form the Medical Monitor

b Results from the screening genotype report and confirmed eligibility must be obtained before proceeding with Day 1 Visit. Local genotype at the Screening Visit is acceptable for enrollment upon review by the Sponsor. A single 14 day extension to the screening window may be granted with permission form the Medical Monitor if the genotype results are delayed.

c Randomization and dosing into the Randomized Cohort of Part 1 will begin after the Day 15 safety, efficacy and available PK data from the 10 subjects in the Sentinel Cohort 2 are reviewed.

d Before proceeding into Part 2, subjects who have completed Day 14 of Part 1 (from either the Sentinel or Randomized Cohorts) will discontinue GS-9131 or PTM but remain on their failing regimen until the site is notified of the subject's eligibility to proceed to Part 2. This period shall be no longer than 9 days while awaiting HIV-1 RNA results and the authorization to proceed from Gilead. Once notified of their eligibility into Part 2 of the study, the subject will discontinue their failing regimen before initiating any Part 2 Day 1 study procedures. In the event the plasma HIV-1 RNA test results performed by the central laboratory are delayed, beyond 9 days, a subject may still proceed to Part 2 of the study if the test results from the local laboratory show a reduction in plasma HIV-1 RNA > 0.5 $\log_{10}$ compared to pre-GS-9131 baseline during the 14 days of GS-9131 functional monotherapy in Part 1 of the study.

e All study visits are to be scheduled relative to the Part 2 Day 1 visit date. Visit windows are ± 4 days of the protocol specified date through Week 24, CCI

[redacted]

h ESDD visit to occur within 72 hours of last dose of study drug. Subjects will be asked to continue attending the scheduled study visits through the Week 24 visit even as the subject discontinues study drug.

i Any AE or test showing abnormal results that is believed to have a possible or probable causal relationship with the study drug will be repeated weekly (or as often as deemed prudent by the Investigator) until the abnormality is resolved, returns to baseline (Day 1) value, or is otherwise explained.

j HIV-1 genotype/phenotype testing for subjects with confirmed virologic failure and HIV-1 RNA >200 copies/mL, at early study discontinuation or Week 24. Following virologic rebound, subjects will be asked to return to the clinic (1-3 weeks later) prior to the next scheduled visit or at the next scheduled study visit for a HIV-1 RNA and HIV-1 genotype/phenotype (reverse transcriptase, protease, and integrase) blood draw. Based on the results of this testing, subjects should be managed according to the Virologic Rebound Schema (Section 6.10).

k Collected fasted (no food or drinks, except water, at least 8 hours prior to blood collection) only at Part 1 – Day 1, Part 2 – Day 1, Week 12, and Week 24, CCI [redacted]. Collected non-fasted at all other visits. If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state to draw blood for the assessments.

l Females of childbearing potential only. Urine and serum pregnancy test will be done at Screening and Day 1and a urine pregnancy test on Days 10 and14. If the urine and serum test is positive at screening, the subject will not be enrolled. A positive urine pregnancy test at any visit will be confirmed with a serum test. If the test is positive the subject will be discontinued from the study.

m Hepatitis C Virus (HCFAb) serology. Subjects who are HCVAb positive will have a HCV RNA test performed.

n Timed PK Sample: collected at predose and one within 15 minutes-4 hours post dose **(Part 2 – Weeks 4, 12 and 18)**

o Single Anytime PK Sample: collected without regard to time of dosing **(Part 2 – Weeks 2, 8 and 24)**

p Intensive PK samples will be collected on Part 1 – Day 10 for Sentinel Cohort 1 and Day 14 for Sentinel Cohort 2 and Randomized Cohort. Prior to the administration of study drug, a predose (<5 minutes prior to dosing) blood sample will be collected. **Subjects will then take an observed dose of study drug at the clinic.** Additional blood samples will be collected at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 24 hour post dose.

q [redacted]

r PBMC collection on Day 10 for Sentinel Cohort 1 and Day 14 for Sentinel Cohort 2 and Randomized Cohort: Predose (<5 minutes prior to dosing), 1, 2, 6 and 24 hours post dose.

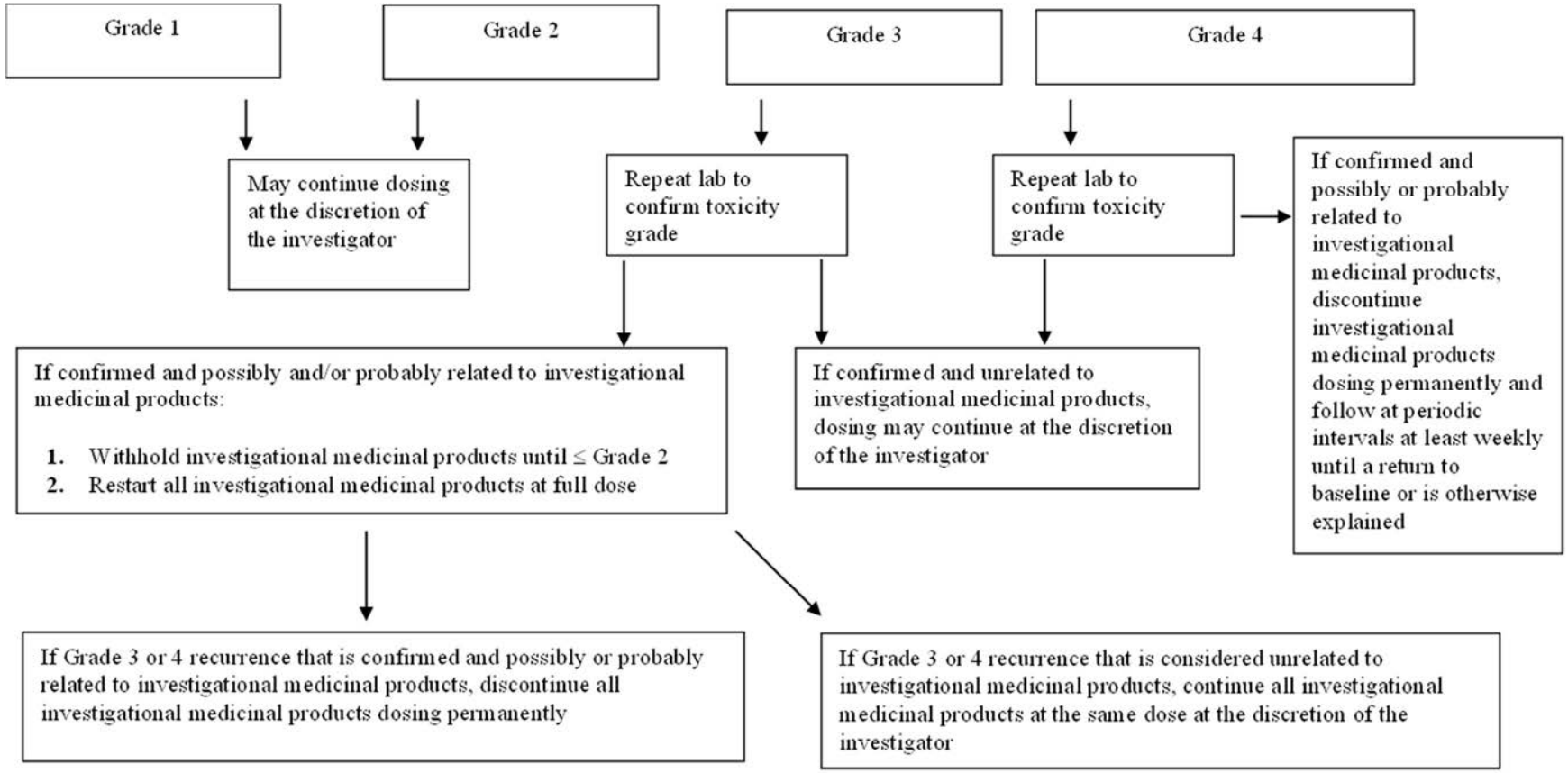
s Randomization may be performed up to 3 days prior to the in-clinic Day 1 visit provided that all screening procedures have been completed, and subject eligibility has been confirmed.

t All study medication in Part 1 will be delivered by directly observed therapy on Days 1-14.

u Subjects must be reminded to take study drug at the same time each day except on days with Timed PK sample and Intensive PK.

v For female subject post-menopausal for less than two years, if FSH <40 mIU/ mL a serum pregnancy test will be required

Appendix 4. Management of Clinical and Laboratory Adverse Events



Appendix 5. GSI 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 (ANC) **Adult and Pediatric, ≥ 7 Months#**	1000 to 1300/mm^3 1.00 to 1.30 GI/L	750 to < 1000/mm^3 0.75 to < 1.00 GI/L	500 to < 750/mm^3 0.50 to < 0.75 GI/L	< 500/mm^3 < 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	100,000 to < 125,000/mm^3 100 to < 125 GI/L	50,000 to < 100,000/mm^3 50 to < 100 GI/L	25,000 to < 50,000/mm^3 25 to < 50 GI/L	< 25,000/mm^3 < 25 GI/L
WBCs	2000/mm^3 to 2500/mm^3 2.00 GI/L to 2.50 GI/L	1,500 to < 2,000/mm^3 1.50 to < 2.00 GI/L	1000 to < 1,500/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 (PT)	> 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 (INR)	1.1 to 1.5 x ULN	>1.5 to 2.0 x ULN	>2.0 to 3.0 x ULN	>3.0 x ULN
Activated Partial Thromboplastin Time (APTT)	> 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%

An overlap between the Grade 1 scale and the Lab's normal range for absolute neutrophils may result for pediatric subjects. Please follow the Gilead convention of grading any result within the LLN and ULN a 0.

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 mmolL	2.0 to < 2.5 mEq/L 2.0 t o <2.5 mmolL	< 2.0 mEq/L <2.0 mmolL
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*) **Adult and Pediatric ≥2 Years**	7.8 <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 -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 mmolL	6.1 to <7.0 mg/dL 1.51 to < 1.74 mmolL	< 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*) **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 Year–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 (non-hemolytic)	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	1.0 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	1.0 mg/dl to <LLN- 57 µmol to <LLN	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L
Creatinine[**]	> 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/Lto <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 > 8.47–13.55 mmol/L	> 1200 mg/dL > 13.55 mmol/L
LDL (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
LDL (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

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

** An overlap between the Grade 1 scale and the Lab's normal range for creatinine may result for Male subjects >70 yrs. Please follow the Gilead convention of grading any result within the LLN and ULN a 0.

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 **Pediatrics <16 years**	-	2.0 to < LLN g/dL 20 to < LLN g/L	< 2.0 g/dL < 20 g/L	NA
≥ 16 years	3.0 g/dL to < LLN 30 g/L to < LLN	2.0 to < 3.0 g/dL 20 to < 30 g/L	< 2.0 g/dL < 20 g/L	NA

URINALYSIS				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hematuria (Dipstick)	1+	2+	3-4+	NA
Hematuria (Quantitative) See Note below Females	>ULN - 10 RBC/HPF	> 10-75 RBC/HPF	> 75 RBC/HPF	NA
Males	6-10 RBC/HPF	> 10-75 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 Mo 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

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 LLN and ULN should be assigned Grade 0.
- If the severity of a clinical AE could fall under either one of two grades (e.g., the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE.

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cardiac Arrhythmia (general) (By ECG or physical exam)	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)	140–159 mmHg systolic OR 90–99 mmHg diastolic	> 159–179 mmHg systolic OR > 99–109 mmHg diastolic	> 179 mmHg systolic OR > 109 mmHg 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–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
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

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Prolonged PR Interval	PR interval 0.21 to 0.25 sec	PR interval > 0.25 sec	Type II 2nd 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 2nd degree AV block	Type II 2nd 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

RESPIRATORY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Bronchospasm (acute)	FEV1 or peak flow reduced to 70% to 80%	FEV1 or peak flow 50% to 69%	FEV1 or peak flow 25% to 49%	Cyanosis OR FEV1 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

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 two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
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 hr	Persistent episodes of unformed to watery stools OR Increase of 4–6 stools over baseline per 24 hrs.	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 exam) 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)

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 ADD)	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
CNS Ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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
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 weak-ness 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

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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: (pre-existing) 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 pre-existing seizures (non-repetitive) 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)
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 5-20 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

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	BMD t-score or z-score –2.5 to –1.0	BMD t-score or z-score < –2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Pediatric < 21 Years	BMD z-score –2.5 to –1.0	BMD z-score < –2.5	Pathological fracture (including loss of vertebral height)	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

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]

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), > 15 Years **Pediatric ≤ 15 Years**	Erythema OR Induration of 5 × 5 cm to 9 × 9 cm (or 25–81 × cm^2) **Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter**	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2) **Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (eg, upper arm/thigh)**	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage **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) **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

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 (IMB)	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 antiμbial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antiμbial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antiμbial 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.

Appendix 6. Definitions of Stage 3 Opportunistic Illnesses in HIV (CDC Guidelines)

1. Candidiasis of bronchi, trachea, or lungs
2. Candidiasis of esophagus
3. Cervical cancer, invasive
4. Coccidioidomycosis, disseminated or extrapulmonary
5. Cryptococcosis, extrapulmonary
6. Cryptosporidiosis, chronic intestinal (> 1 month duration)
7. Cytomegalovirus disease (other than liver, spleen or nodes)
8. Cytomegalovirus retinitis (with loss of vision)
9. Encephalopathy, HIV-related
10. Herpes simplex: chronic ulcer(s) (> 1 month duration); or bronchitis, pneumonitis or esophagitis
11. Histoplasmosis, disseminated or extrapulmonary
12. Isosporiasis, chronic intestinal (> 1 month duration)
13. Kaposi's sarcoma
14. Lymphoma, Burkitt's (or equivalent term)
15. Lymphoma, immunoblastic (or equivalent term)
16. Lymphoma, primary, of brain
17. *Mycobacterium avium* complex or *Myobacterium kansasii*, disseminated or extrapulmonary
18. *Mycobacterium tuberculosis*, of any site, pulmonary, disseminated or extrapulmonary
19. *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
20. Pneumocystis jirovecii (previously known as "*Pneumocystis carinii*) pneumonia
21. Pneumonia, recurrent
22. Progressive multifocal leukoencephalopathy
23. *Salmonella* septicemia, recurrent
24. Toxoplasmosis of brain
25. Wasting syndrome attributed to HIV infection

CDC Stage-3-Defining Opportunistic Illnesses in HIV Infection - 2014 {Schneider 2008}

Appendix 7. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a female born subject is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming post-menopausal, unless permanently sterile or with medically documented ovarian failure.

Women are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause. In addition, women of any age with amenorrhea of ≥ 12 months may also be considered postmenopausal if their follicle stimulating hormone (FSH) level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age.

2) Contraception Requirements for Female Subjects

a. Study Drug Effects on Pregnancy and Hormonal Contraception

The data on GS-9131 in pregnant women is limited or not available. There is no suspicion of human teratogenicity based on class effects or genotoxic potential. Relevant non-clinical reproductive toxicity studies for human pregnancy do not indicate a strong suspicion of human teratogenicity/fetotoxicity. In female rats, effects on embryo-fetal viability were noted, and effects in humans are unknown. GS-9131 and DRV + RTV have demonstrated/suspected or have insufficient data to exclude the possibility of a clinically relevant interactions with hormonal contraception that results in reduced contraception efficacy. Therefore, contraceptive steroids are not recommended as a contraceptive method either solely or as a part of a contraceptive regimen. Please refer to the latest version of the investigator's brochure for additional information.

b. Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of highly effective contraceptive measures. They must also not rely on hormone-containing contraceptives as a form of birth control during the study. They must have a negative serum pregnancy test at Screening and a negative pregnancy test on the Baseline/Day 1 visit prior to randomization. Pregnancy tests will be performed as defined in the protocol. A pregnancy test will be performed at the end of systemic exposure after the last study drug dose. In the event of a delayed menstrual period (over one month between menstruations), a pregnancy test must be performed to rule out pregnancy. This is even true for women of childbearing potential with infrequent or irregular periods. Female subjects must agree to one of the following from Screening until 30 days following the end of relevant systemic exposure.

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

Or

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

  — Intrauterine device (IUD) with a failure rate of <1% per year

  — Tubal sterilization

  — Essure micro-insert system (provided confirmation of success 3 months after procedure)

  — Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until at least 30 days after the end of relevant systemic exposure.

3) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). Female condom and male condom should not be used together.

4) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 30 days of last study drug dose. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. Instructions for reporting pregnancy, and pregnancy outcome are outlined in Section 7.7.2.1.

Appendix 8. Prior and Concomitant Medications For Subjects in Sentinel Cohort 1 and Sentinel Cohort 1 Subjects Who Go on to Part 2: bictegravir GS-9131 + BIC + DRV + RTV

Subjects receiving oral contraceptives or patch contraceptives must consider other methods of contraception as concentrations of ethinyl estradiol, norgestimate or norethindrone may increase or decrease upon coadminstration with study drug.

Concomitant use of some medications and herbal/natural supplements with study drug may result in pharmacokinetic interactions resulting in increases or decreases in exposure of study drugs or these medications.

Medications listed in the following table and herbal/natural supplements are excluded or should be used with caution while subjects are participating in the study. During Part 1 of the study, physicians should also refer to the prescribing information for the current background regimen in addition to the recommendations listed in the table below. Subjects should discontinue disallowed concomitant medications 30 days prior to initiation of study drug.

Prior and Concomitant Medications

Drug Class	Agents Disallowed*	Agents To Be Used With Caution
Acid Reducing Agents Antacids Buffered Medications		Concentration of study drug (BIC) may decrease with antacids. Subjects may not take antacids (e.g,, Tums, or Rolaids); the ulcer medication sucralfate (Carafate); or vitamin or mineral supplements that contain calcium, iron or zinc for a minimum of 6 hours before and 2 hours after any dose of study medication.
Alpha 1-adrenoreceptor antagonist	Alfuzosin	
Analeptic	Modafinil	
Analgesics		Propoxyphene: Concentrations may increase with study drug(s); clinical monitoring is recommended.

Drug Class	Agents Disallowed*	Agents To Be Used With Caution
Antiarrhythmic Agent	Dofetilide, Dronedarone, Amiodarone, Bepridil, Quinidine, Systemic Lidocaine	Flecainide, Propafenone, Mexilitine, Disopyramide: Concentrations may increase with study drug(s). Therapeutic concentration monitoring, if available, is recommended for antiarrhythmics when coadministered with study drug(s). Digoxin The lowest dose of digoxin should initially be prescribed. The serum digoxin concentrations should be monitored and used for titration of digoxin dose to obtain the desired clinical effect.
Anti-anginal	Ranolazine	
Antibacterials		No dose adjustment is needed when co-administered with study drug(s) for patients with normal renal function. For co-administration of clarithromycin and study drug(s) in patients with renal impairment, the following dose adjustments should be considered: • For subjects with CLcr of 30-60 mL/min, the dose of clarithromycin should be reduced by 50% • For subjects with CLcr of <30 mL/min, the dose of clarithromycin should be reduced by 75%
Anticoagulants		Apixaban, Rivaroxaban: Use with study drug is not recommended. Dabigatran Etexilate: Concomitant use with dabigatran etexilate is not recommended in specific renal impairment groups (depending on the indication). Please see the dabigatran prescribing information for specific recommendations. Warfarin: Concentrations may be affected by study drug(s); frequent INR (International Normalized Ratio) monitoring is recommended.
Anticonvulsants	Phenobarbital, Phenytoin, Carbamazepine, Oxcarbazepine	Clonazepam, Ethosuximide, Concentrations may increase with study drug(s). Divalproex, Lamotrigine: Concentrations may be affected by study drug(s). Clinical monitoring is recommended.

Drug Class	Agents Disallowed*	Agents To Be Used With Caution
Antidepressants		SSRIs, TCAs or trazodone: When coadministering with study drug, careful dose titration of the antidepressant to the desired effect, including using the lowest feasibly initial or maintenance dose, and monitoring for antidepressant response are recommended.
Antifungals		Monitor for increased study drug adverse reactions with concomitant use of itraconazole, ketoconazole or posaconazole Ketoconazole and Itraconazole: When co-administration of required, the daily dose of ketoconazole or itraconazole should not exceed 200 mg with monitoring for increased antifungal adverse events. Co-administration of voriconazole is not recommended unless benefit/risk assessment justifies the use of voriconazole. Subjects receiving antifungals should be monitored for adequate clinical response.
Anti-Gout	Cochicine (in subjects with renal or hepatic impairment), Probenecid	For subjects without renal or hepatic impairment: • Treatment of gout flares - co-administration of colchicine: 0.6 mg (1 tablet) x 1 dose followed by 0.3 mg (half tablet) 1 hour later. Treatment course to be repeated no earlier than 3 days. • Prophylaxis of gout flares - co-administration of colchine: If the original regimen was 0.6 mg twice a day, the regimen should be adjusted to 0.3 mg once a day. If the original regimen was 0.6 mg once a day, the regimen should be adjusted to 0.3 mg once every other day. • Treatment of familial Mediterranean fever – coadministration of colchicine: Maximum daily dose of 0.6 mg (given as 0.3 mg twice a day)
Anti-malarial		Artemether/lumefantrine: Monitor for potential decrease of antimalarial efficacy or potential QT prolongation
Antihistamines	Astemizole, Terfenadine	

Drug Class	Agents Disallowed*	Agents To Be Used With Caution
Antimycobacterials	Rifampin, Rifapentine, Rifabutin	
Anti-psychotic	Lurasidone, Pimozide, Quetiapine	Perphenazine, Risperidone, Thioridazine: A dose decrease in anti-psychotics that are metabolized by CYP3A or CYP2D6 may be needed when co-administered with study drug.
Antiretrovirals	Any antiretroviral drug that is not part of the study regimen	
B-blockers		Clinical monitoring is recommended for con-administration with beta blockers that are metabolized by CYP2D6 (e.g., metoprolol, timolol). A dose decrease may be needed for these drugs when co-administered with study drug(s), and a lower dose of the beta blocker should be considered.
Calcium Channel Blockers	Bepridil	Clinical monitoring is recommended for co-administration with calcium channel blockers metabolized by CYP3A (e.g., felodipine, nifedipine, verapamil, diltiazem, amlodipine)
Corticosteroids: Inhaled/Nasal		Concomitant use of inhaled or nasal fluticasone or other corticosteroids (e.g., budesonide) that are metabolized by CYP3A and study drug(s) may result in reduced serum cortisol concentrations. Alternatives should be considered, particularly for long term use.
Corticosteroids: Systemic	All agents, including dexamethasone	Use of Prednisone as a steroid burst (≤1 week of use) should be monitored appropriately. Co-administration with dexamethasone or other corticosteroids that induce CYP3A may result in loss of therapeutic effect of and development of resistance to study drug. Co-administration of study drug with corticosteroids that are metabolized by CYP3A, particularly for long term use, may increase the risk for development of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression. Consider the potential benefit of treatment versus the risk of systemic corticosteroid effects.

Drug Class	Agents Disallowed*	Agents To Be Used With Caution
Endothelin receptor antagonists		Bosentan: Initiation of bosentan in subjects taking study drug: In subjects who have been receiving study drug for at least 10 days, start bosentan at 62.5 mg once daily or every other day based upon individual tolerability. Initiation of study drug in subjects on bosentan: Discontinue use of bosentan at least 36 hours prior to initiation of study drug. After at least 10 days following initiation of study drug, resume bosentan at 62.5 mg once daily or every other day based upon individual tolerability.
Ergot Derivatives	Dihydroergotamine, Ergotamine, Ergonovine, Methylergonovine, Ergometrine	
GI Motility Agents	Cisapride	
Herbal/Natural Supplements	St. John's Wort, Echinacea	
HMG-CoA Reductase Inhibitor	Lovastatin, Simvastatin	Atorvastatin, fluvastatin, pitavastatin, rosuvastatin, pravastatin: Concentrations may increase with study drug(s). Start with the lowest recommended dose and titrate while monitoring for safety. Do not exceed atorvastatin 20 mg/day.
Oral Contraceptives		Effective and alternative (non-hormonal) forms of contraception should be considered.
Inhaled beta agonist		Salmeterol: Coadministration with study drug(s) may result in increased plasma concentrations of salmeterol, which is associated with the potential for serious and/or life threatening reactions. Coadministration is not recommended.
Narcotic analgesics metabolized by CYP3A:		Fentanyl, oxycodone: Careful monitoring of therapeutic effects and adverse reactions associated with CYP3A-metabolized narcotic analgesics (including potentially fatal respiratory depression) is recommended with co-administration with study drug. Tramadol: A dose decrease may be needed for tramadol with concomitant use.

Drug Class	Agents Disallowed*	Agents To Be Used With Caution
Narcotic analgesic for treatment of opioid dependence:		No dose adjustment for buprenorphine or buprenorphine/naloxone is required with concurrent administration of study drug(s). Clinical monitoring is recommended if study drug(s) and buprenorphine or buprenorphine/naloxone are coadministered. No adjustment of methadone dosage is required when initiating co-administration of study drug(s). However, clinical monitoring is recommended as the dose of methadone during maintenance therapy may need to be adjusted in some patients. Meperidine (Pethidine): Dosage increase and long-term use are not recommended due to increased levels of metabolite normeperidine, which has analgesic and CNS stimulant (e.g., seizures) activities.
PDE-5 Inhibitor	Sildenafil for treatment of PAH	Avanafil: Co-administration with avanafil is not recommended. Tadalafil: Initiation of tadalafil in subjects taking study drug: In subjects receiving study drug for at least one week, start tadalafil at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability. Initiation of study drug in subjects taking tadalafil: Avoid use of tadalafil during the initiation of study drug. Stop tadalafil at least 24 hours prior to starting study drug. At least one week following the initiation of study drug, resume tadalfil at 20 mg once daily. Increase to 40 mg once daily based upon individual tolerability. Use of PDE-5 inhibitors for erectile dysfunction: Sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg in 72 hours, or tadalafil at a single dose not exceeding 10 mg in 72 hours can be used with increased monitoring for PDE-5 inhibitor –associated adverse reactions.
Proton pump inhibitor: Omeprazole		When omeprazole is co-administered with study drug(s), monitor patients for decrease efficacy of omeptrazole. Consider increasing the omeprazole dose in patients whose symptoms are not well controlled; avoid use of more than 40 mg per day of omeprazole.

Drug Class	Agents Disallowed*	Agents To Be Used With Caution
Sedative/hypnotic	Orally administered Midazolam, Triazolam	Buspirone, Clorazepate, Diazepam, Estazolam, Flurazepam, Zolpidem: A lower dose should be considered and dose titration is recommended. Monitoring for increased and prolonged effects or adverse reactions is recommended.

Should subjects have a need to initiate treatment with any excluded concomitant medication, the Gilead Medical Monitor must be consulted prior to initiation of the new medication. In instances where an excluded medication is initiated prior to discussion with the Sponsor, the Investigator must notify Gilead as soon as he/she is aware of the use of the excluded medication.