CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1b, Randomized, Double-Blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of GS-9620 in Antiretroviral Treated HIV-1 Infected Controllers	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404	
IND Number:	122452	
EudraCT Number:	Not Applicable	
Clinical Trials.gov Identifier:	NCT03060447	
Indication:	HIV-1 Infection	
Protocol ID:	GS-US-382-3961	
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CONFIDENTIALITY STATEMENT

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
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Study Title:	A Phase 1b, Randomized, Double-Blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of GS-9620 in Antiretroviral Treated HIV-1 Infected Controllers
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	122452 Not Applicable NCT03060447
Study Centers Planned:	Multiple centers in North America
Objectives:	The primary objective of this study is: • To evaluate the safety and tolerability of a 10-dose regimen of GS-9620 in HIV-1 infected controllers on antiretroviral treatment (ART) and during analytical treatment interruption (ATI) following GS-9620 dosing The secondary objectives of this study are: <u>Virology</u> • To evaluate the effect of GS-9620 in reactivating the HIV-1 reservoir, as measured by changes in plasma HIV-1 RNA by Taqman 2.0 • To evaluate the effect of GS-9620 in modulating time to virologic rebound and plasma viral load set-point following ATI <u>Immunology/Pharmacodynamics</u> • To evaluate the pharmacodynamics (PD) of GS-9620 as measured by changes in serum/plasma cytokines, and mRNA of interferon-stimulated genes (ISGs) in whole blood • To evaluate effects of GS-9620 on immune cell activation in whole blood <u>Pharmacokinetics</u> • To evaluate the plasma pharmacokinetics (PK) of GS-9620

Study Design:

This is a randomized, double-blind study with a single cohort of HIV-1 infected controllers on ART with a history of pre-ART plasma HIV-1 RNA between 50 and ≤5,000 copies/mL.

Randomization will be stratified by pre-ART viral load (≥50 to < 2,000 copies/mL or ≥2,000 to ≤5,000 copies/mL) at screening.

The study will be conducted in three periods. In **Period 1**, up to 30 subjects will be randomized 2:1 to receive GS-9620 or placebo-to-match. All subjects will receive a total of 10 doses of their assigned study treatment administered orally once every 14 days. Subjects will continue to take their ART.

In **Period 2**, all subjects will discontinue ART and be monitored for rebound in HIV-1 plasma viremia for **24** weeks of close observation and follow up.

For the 24 weeks of ATI, subjects will be seen weekly (ATI Visits 1-24).

Subjects who restart ART during Period 2 will complete ART Re-Initiation Visits, and then Post ART Re-Suppression Visits monthly for 6 additional months (Post ART Re-Suppression Visits 1-6). For these subjects, the last study visit will be the Post ART Re-Suppression Visit 6.

Subjects who complete 24 weeks of ATI without restarting ART will move onto **Period 3**. CCI [redacted]

CCI [redacted]

B) If subjects restart ART at the start of Period 3, subjects will complete ART Re-Initiation Visits, and then Post ART Re-Suppression Visits monthly for 6 additional months (Post ART Re-Suppression Visits 1-6). For these subjects, the last study visit will be the Post ART Re-Suppression Visit 6.

Number of Subjects Planned:

Up to 30 subjects in total; randomized 2:1 to receive GS-9620 or placebo-to-match.

Subjects who discontinue study participation before completion of dosing for reasons other than study treatment-related adverse events (AEs) may be replaced.

Target Population:	HIV-1 infected male and non-pregnant, non-lactating female adults who have a documented history of controlling plasma HIV-1 RNA between 50 and ≤5,000 copies/mL prior to ART initiation and who have been virologically suppressed (HIV-1 RNA <50 copies/mL) on ART for at least 6 months prior to screening.
Duration of Treatment:	Subjects will receive up to 10 doses of GS-9620 or placebo-to-match over a minimum of a 20-week period (Period 1), followed by 24 weeks of close observation post ATI start (Period 2). For subjects who re-initiate ART during Period 2, duration of study will extend for 6 months following virologic re-suppression on ART (Post ART Re-suppression Visits 1-6). After 24 weeks of ATI, subjects will CCI restart ART CCI [redacted] (Period 3). Subjects who restart ART will complete ART Re-Initiation Visits and then will complete Post ART Re-Suppression Visits monthly for 6 additional months. For these subjects, the last study visit will be Post ART Re-Suppression Visit 6. CCI [redacted] The End of Study visit will occur one week after the last ATI visit.
Diagnosis and Main Eligibility Criteria:	HIV-1 infected subjects who meet the following criteria: • Age ≥ 18 years of age • Plasma HIV-1 RNA levels <50 copies/mL at Screening • Chronic HIV-1 infection (for ≥6 months) prior to ART initiation • Pre-ART Plasma HIV-1 RNA set point between 50 and ≤5,000 copies/mL measured within two years prior to ART initiation calculated as below: — At least one plasma HIV-1 RNA level, while off ART, above the level of detection using standard assays (<40 copies/mL Abbott, <50 copies/mL Roche, <75 copies/mL bDNA) and ≤5,000 copies/mL prior to ART initiation. — Using all available viral load determinations during the two years prior to ART, the mean HIV-1 RNA viral load (defined as viral load set point) must be above the limit of detection and ≤5,000 copies/mL (those determinations below the level of quantification will be considered as detectable at this threshold level). Two years of prior data are not required but up to two years of data will be evaluated.

- On ART for ≥6 months prior to screening
  - — The following agents are allowed as part of the current ART regimen: NRTIs, raltegravir, dolutegravir, rilpivirine, and maraviroc
  - — A change in ART regimen ≥45 days prior to Pre-baseline/Day -13 for reasons other than virologic failure (e.g., tolerability, simplification, drug-drug interaction profile) is allowed
- Documented plasma HIV-1 RNA < 50 copies/mL for ≥ 6 months preceding the Screening visit (or undetectable HIV-1 RNA level according to the local assay being used if the limit of detection is ≥ 50 copies/mL).
- Unconfirmed virologic elevations of ≥ 50 copies/mL (transient detectable viremia, or "blip") prior to screening are acceptable. (If the lower limit of detection of the local HIV-1 RNA assay is < 50 copies/mL, the plasma HIV-1 RNA level cannot exceed 50 copies/mL on two consecutive HIV-1 RNA tests)
- If ART regimen is changed ≥ 45 days prior to Pre-baseline/ Day -13, plasma HIV-1 RNA <50 copies/mL at Pre-baseline/ Day -13 visit is required
- No documented history of resistance to any components of the current ART regimen
- Availability of a fully active alternative ART regimen, in the opinion of the Investigator, in the event of discontinuation of the current ART regimen with development of resistance.
- Hemoglobin ≥ 11.5 g/dL (males) or ≥ 11 g/dL (females)
- White Blood Cells ≥ 2,500 cells/μL
- Platelets ≥ 125,000/mL
- Absolute Neutrophil Counts ≥ 1,000 cells/μL
- CD4+ count ≥ 500 cells/μL
- Alanine aminotransferase (ALT), aspartate aminotransferase (AST) or bilirubin ≤ 2 × upper limit of normal (ULN)
- Estimated glomerular filtration rate ≥ 60 mL/min
- No autoimmune disease requiring on-going immunosuppression
- No evidence of current HBV infection

- No evidence of current HCV infection (positive anti-HCV antibody and negative HCV PCR results are acceptable)
- No documented history of pre-ART CD4 nadir < 200 cells/μL (unknown pre-ART CD4 nadir is acceptable)
- No history of opportunistic illness indicative of stage 3 HIV
- No acute febrile illness within 35 days prior to Pre-Baseline/ Day -13

Study Procedures/ Frequency:

The main study phase (Period 1 and Period 2) consists of a screening period of up to 35 days, a pre-treatment period of 14 days (from Day -13 to Day 1), a treatment period of up to 10 doses (from Dose 1-Day 1 to Dose 10-Day 1) administered orally every 14 days, a period of 24 weeks of close observation post ATI start beginning on Dose 10-Day 28, additional follow up visits (either ART Re-Initiation Visits with Post ART Re-Suppression Visits CCI [redacted]), and an End of Study Visit (if applicable). Enrolled subjects will undergo the following scheduled study visits.

Period 1:

Pre-Baseline/Day -13, may include tissue sampling

Baseline/Dose 1-Day 1, Dose 1-Day 2, Dose 1-Day 8

Dose 2-Day 1, Dose-2-Day 8

Dose 3-Day 1, Dose 3-Day 8

Dose 4-Day 1, Dose 4-Day 2, Dose 4-Day 4, Dose 4-Day 8

Dose 5-Day 1, Dose 5-Day 8

Dose 6-Day 1, Dose 6-Day 4, Dose 6-Day 8

Dose 7-Day 1, Dose 7-Day 8

Dose 8-Day 1, Dose 8-Day 8

Dose 9-Day 1, Dose 9-Day 8

Dose 10-Day 1, Dose 10-Day 2, Dose 10-Day 4, Dose 10-Day 8, Dose 10-Day 14 (may include tissue sampling)

If HIV-1 RNA viral load is >5,000 copies/mL at any visit post Dose, viral load will be observed at next scheduled visit or retested within 4 days. The next dose will be withheld and only given if a viral load of ≤5,000 copies/mL is achieved. The study procedure schedule will be reset relative to the next dose of GS-9620.

Subjects who prematurely discontinue study drug prior to completing Dose 10 will be required to complete an Early Study Drug Discontinuation Visit within 30 days after their last dose.

Period 2:

ATI Visit 1 (Beginning of **analytical treatment interruption, 28 days after Dose 10**) subjects will discontinue ART.

Subjects will be closely observed for a 24 week ATI period during which plasma HIV-1 RNA values, CD4+ cell count, CD8+ cell count, CD4/CD8 ratio and CD4 % will be measured once a week.

Viral Remission

After the first 12 weeks of ATI are complete, an additional ATI Remission Visit (may include tissue sampling) may be scheduled. This visit will be completed once HIV-1 RNA is <50 copies/mL.

Viral Rebound

During the 24 week ATI period, if plasma HIV-1 RNA becomes > 50 copies/mL, the visit schedule for HIV-1 RNA measurements may be adjusted per Investigator's discretion.

ART Restart Criteria

During 24-week ATI period CCI [redacted], ART will be re-initiated if any of the criteria below are met:

- if HIV-1 RNA is >10,000 copies/mL on four consecutive weekly measurements OR
- if HIV-1 RNA does not decrease to <1,000 copies/mL within 6 weeks of virologic rebound OR
- if CD4+ cell count is confirmed to decrease by >30% from pre-ATI levels OR
- if CD4+ cell count is confirmed<350 cells/µL OR
- Per Investigator or Sponsor's discretion due to other clinical criteria

ART Restart Measurements

Following ART re-initiation, weekly visits measuring plasma HIV-1 RNA, CD4+ cell count, CD8+ cell count, CD4/CD8 ratio and CD4% will be conducted.

If plasma viral load becomes undetectable (<50 copies/mL); then monitoring measurements will be every other week for two consecutive measures then once a month for 6 months.

At Post-ART Re-suppression Visit 6, HIV-1 reservoir will be measured by plasma SCA, CAVR, CAVD CCI [redacted]. The subject will end the study at this visit.

If plasma viral load is ≥200 copies/mL for four weeks then resistance testing will be performed at the next visit per Management of Virologic Failure post ART Restart (Section 6.9.3).

Period 3:

After 24 weeks of ATI, subjects will CCI restart CCI [redacted] ART.

Subjects who restart ART will complete ART Re-Initiation Visits and then will complete Post ART Re-Suppression Visits monthly for 6 additional months. For these subjects, the last study visit will be Post ART Re-Suppression Visit 6.

CCI [redacted]

Screening Procedures:

Screening procedures include: complete physical examination, vital signs, height, weight, medical history (including route and estimated duration of HIV infection, pre-ART viral load set point, and complete ART history), HIV-1 RNA, hematology, serum chemistry, CD4+ cell count, CD8+ cell count, CD4/CD8 ratio, CD4%, serum pregnancy test (for females of childbearing potential), HBV and HCV serologies, eGFR, urinalysis, plasma ART trough PK collection, and electrocardiogram (ECG). Screening procedures also include collection of HLA class I and II type if not available through historical reports. Pre-ART CD4 nadir, and historical genotype will be collected, if available.

In order to establish eligibility, Investigators may repeat screening procedures or laboratory assessments for subjects who have an acute illness or abnormal laboratory value that is expected to resolve without sequelae within the screening window.

On-Study Procedures:

Dosing:

Dosing will occur 14 days apart starting at Dose 1-Day 1, Dose 2-Day 1, Dose 3-Day 1, Dose 4-Day 1, Dose 5-Day 1, Dose 6-Day 1, Dose 7-Day 1, Dose 8-Day 1, Dose 9-Day 1 and Dose 10-Day 1 visits respectively. Subjects will fast for at least 2 hours (preferably overnight) before dosing. Subjects will also be asked to provide information on food consumption and total fasting time prior to dosing.

The Investigator will verify the subject's continued eligibility for dosing at post Baseline/Dose 1-Day 1 dosing visits, including the absence of dose-limiting toxicities (DLTs) and a negative urine pregnancy test (for females of childbearing potential), prior to dosing. All doses will be directly administered by blinded site staff. Subjects will fast for 2 hours after dosing.
After Dose 1 on Day 1, subjects will remain on site for 10 hours after dosing for safety assessment and phlebotomy.

Safety:

Solicitation of AEs and concomitant medications at every visit.

Symptom-directed physical examination at every visit during Period 1. Complete physical examination once a month and symptom directed physical examination on other visits to occur every two weeks during Period 2 CCI [redacted]

Hematology, serum chemistry, and urinalysis at all dosing visits, monthly during Period 2 CCI [redacted], post ART Re-suppression Visits and Early Study Drug Discontinuation Visit.

Urine pregnancy test (for females of childbearing potential) prior to each dose, at ATI visit 1 (ATI start visit), at every other visit thereafter during Period 2, CCI [redacted], at first ART Re-initiation visit and monthly thereafter until Post ART Re-Suppression Visit 1, post ART Re-suppression Visits and End of Study Visit.

Vital signs (blood pressure, pulse, respiration rate and temperature) at all dosing visits and every other week during Period 2 CCI [redacted].

Subjects will be instructed to contact the site immediately if any flu-like symptoms are noted (e.g., fatigue, pyrexia, chills, myalgia, joint pain or headache).

Pharmacokinetics:

Plasma GS-9620 concentrations: blood collection at Pre-dose (≤ 5 minutes prior to dosing), 0.5, 1, 2, 4, 6, 8, 10 and 24 hours post dose at Dose 1-Day 1 visit.

Plasma ART concentrations: a single trough PK sample will be collected at Screening. The timing of the ART trough collection is to be 20-24 hours following the subject's previous QD regimen dose (and, for any subject on a regimen containing a BID component, the trough collection must also occur 8-12 hours following the subject's previous dose of that BID component). Another single trough PK sample will be collected at Dose 6 Day 4. These samples may be analyzed to assess ART adherence.

Additional PK samples may be drawn to verify that subject continues to be off-ART during the ATI phase (Period 2 CCI [redacted]). Samples will be drawn upon Sponsor request depending on the subject's HIV-1 RNA levels.

Pharmacodynamics:

Whole blood ISG mRNA panel: within 1 hour before and 1 day after Doses 1, 4, 10 of study drug.

TLR7 genotyping: at Pre-Baseline/Day -13

CCI [redacted]

Changes in the levels of serum/plasma cytokines/chemokines by immunoassays: within 1 hour before and 1 and 7 days after Doses 1, 4, and 10, and ATI Remission Visit.

Virology:

Plasma HIV-1 RNA: at every visit.

CAVR and CAVD from PBMCs: at Pre-baseline/Day -13 and within 1 hour before and 1 and 3 days after Doses 4 and 10, within 1 hour before and 3 days after Dose 6, Dose 10-Day 14, ATI Remission Visit and at Post-ART re-suppression Visit 6 (6 months post-ART virologic re-suppression).

Plasma HIV-1 RNA Single Copy Assay (SCA) from plasma: at Pre-Baseline/Day -13, within 1 hour before, and 1 and 3 days after Doses 4 and 10, within 1 hour before and 3 days after Dose 6, Dose 10-Day 14, ATI Remission Visit and Post-ART re-suppression Visit 6 (6 months post-ART virologic re-suppression).

CCI [redacted]

CCI [redacted]

[redacted]

Immunology:

CCI [redacted]

HIV-specific T-cell responses from PBMC by intracellular cytokine staining (ICS): at Pre-Baseline/Day -13, Dose 10-Day 14, and ATI Remission Visit.

HIV-specific antibody profiling from serum: at Pre-Baseline/Day -13, Dose 10-Day 14, and ATI Remission Visit.

CCI [redacted]

CCI [redacted]

[redacted]

Additional End of Study Procedures:

Symptom-directed physical examination, review of AEs and concomitant medications, vital signs, weight, eGFR, hematology, serum chemistry, urine pregnancy test and urinalysis

Early Study Drug Discontinuation Visit Procedures:

Symptom-directed physical examination, review of AEs and concomitant medications, vital signs, weight, eGFR, HIV-1 RNA, hematology, serum chemistry, whole blood ISG mRNA panel, serum cytokine/soluble biomarker studies, urinalysis, urine pregnancy test.

	Procedure Definitions and Specifications: HIV-1 RNA will be performed by a validated assay with a lower limit of quantitation of at least 50 copies/mL. **Hematology** panel includes: complete blood count (CBC) with differential and platelets, CD4+ cell count, CD8 cell count, CD4/CD8 ratio and CD4%. **Serum chemistry** panel includes: alkaline phosphatase, AST, ALT, total and direct bilirubin, total protein, albumin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphate, magnesium, potassium, sodium, CPK, and uric acid. **Urinalysis** includes dipstick. CCI [redacted] **Serum and urine pregnancy tests** are performed only on female subjects of childbearing potential. **Phlebotomy volume limits** will be maintained in accordance with American Red Cross blood donation guidelines, which limit blood donation to 473 mL every 56 days. Subjects will undergo periodic phlebotomy over study period and will provide no more than 473 mL every 56 days. Subjects will be prohibited from blood donation in excess of that required for clinical care within 30 days prior to screening and 30 days after study ends. HIV-1 seronegative sexual partners of enrolled study subjects may be referred to a local HIV Pre-Exposure Prophylaxis (PrEP) clinic for HIV risk assessment evaluation.
Test Product, Dose, and Mode of Administration:	GS-9620 8 mg dose, administered as four 2 mg tablets orally every 14 days (window of ± 1 day).
Reference Therapy, Dose, and Mode of Administration:	Placebo-to-match GS-9620, administered orally every 14 days (window of ± 1 day).
Duration of Treatment:	Subjects will be treated to receive up to 10 doses of GS-9620 or placebo-to-match.
Other Treatment:	Subjects will continue their existing ART regimen (as currently prescribed and supplied) for the duration of study Period 1 and then undergo ATI four weeks after the final (tenth) dose of GS-9620 or placebo-to-match.

Criteria for Evaluation:

Safety:	Adverse events and clinical laboratory tests
Virology:	Plasma log_{10} HIV-1 RNA Plasma HIV-1 RNA by SCA PBMC, CCI [redacted] PBMC associated viral reservoir measurements Time to HIV-1 viral rebound during ATI Peak HIV-1 viral load during ATI Plasma HIV-1 viral set point during ATI
Pharmacodynamics:	Serum/plasma cytokines/chemokines Whole blood ISG mRNAs CCI [redacted]
Immunology:	Immune cell frequency, CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted]

Statistical Methods:

Safety:	The incidences of treatment-emergent AEs and treatment-emergent laboratory abnormalities will be summarized by treatment group. The proportion of subjects in each treatment group with an AE leading to premature discontinuation of study drug and proportion of subjects with serious adverse events (SAEs) will be summarized by treatment group.
Virology:	The change in plasma HIV-1 RNA and the incidence of detectable plasma HIV-1 RNA by Taqman 2.0 at each visit will be summarized by treatment group. Time to viral rebound during ATI will be summarized by treatment group.

	The difference in plasma viral set point between pre-ART values and given time points (including but not limited to): prior to ART restart in Period 2 and 3, and ATI Remission Visit will be summarized by treatment group. The peak HIV-1 viral load during Period 2 or 3 will be summarized by treatment group. The change in plasma HIV-1 RNA by SCA may be explored. CCI [redacted]
Pharmacodynamics:	The changes in serum/plasma cytokines and mRNA of ISGs in whole blood will be summarized using descriptive statistics by treatment group. CCI [redacted] The type of TLR7 genotype may be reported and its association with key parameters may be explored.
Immunology:	The changes in immune cell activation in whole blood will be summarized using descriptive statistics by treatment group. The change in immune cell frequency and phenotyping may be explored. The change in magnitude and polyfunctionality of HIV-1-specific T cell immune responseCCI [redacted]
Pharmacokinetics:	The plasma pharmacokinetics (PK) of GS-9620 will be evaluated.
Sample Size:	This is an exploratory study to characterize the safety and efficacy of GS-9620; therefore, no power calculation was performed. Up to 20 subjects receiving GS-9620 will provide a preliminary assessment of safety and efficacy.

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	degree(s) Celsius
°F	degree(s) Fahrenheit
Ab	Antibody
ACAT	Acetyl-coenzyme A acetyltransferase
ACE	Angiotensin Converting Enzyme
ACTG	AIDS Clinical Trials Group
ADCC	Antibody dependent T cell-mediated cytotoxicity
ADCP	Antibody dependent T cellular phagocytosis
AE	adverse event
AIDS	Acquired Immune Deficiency Syndrome
ALT	alanine aminotransferase (SGPT)
ANOVA	analysis of variance
ART	antiretroviral therapy
AST	aspartate aminotransferase (SGOT)
ATI	analytical treatment interruption
AUC_{0-t}	area under the plasma concentration-time curve from zero
AUC_{24h}	area under the plasma concentration-time curve in 24 hours
AUC_{tau}	area under the plasma concentration versus time curve over the dosing interval (tau)
BID	*bis in die* (two-or twice-a-day)
BLQ	below the limit of quantitation
BUN	blood urea nitrogen
CAVD	cell-associated viral DNA
CAVR	cell associated viral RNA
CBC	complete blood count
CD	Cluster of Differentiation
CDC	Center for Disease Control and Prevention
CFR	Code of Federal Regulations (United States)
CHB	Chronic hepatitis B
C_{last}	last observed quantifiable concentration of the drug
CL_{cr}	creatinine clearance
C_{max}	maximum observed concentration of drug
CNS	central nervous system
CPK	creatine phosphokinase (= creatine kinase, CK)
CSR	clinical study report
C_{tau}	observed drug concentration at the end of the dosing interval (tau)
CYP3A	cytochrome P450
DHHS	Department of Health and Human Services
dL	deciliter(s)
DLT	dose-limiting toxicities
DNA	deoxyribonucleic acid
PVE	Pharmacovigilance and Epidemiology (PVE), Gilead Sciences

DTG	Dolutegravir
EC	ethics committee
EC_{50}	50% effective inhibitory concentration
ECG	Electrocardiogram
eCRF	electronic case report form(s)
EDC	Electronic data capture
eGFR	estimated glomerular filtration rate
ESDD	Early Study Drug Discontinuation
EudraCT	European Union Drug Regulating Authorities Clinical Trials
ET	Early termination
FAS	Full analysis set
FDA	Food and Drug Administration (United States)
FSH	Follicle stimulating hormone
FTC	Emtricitabine
g	Gram
GALT	gut associated lymphoid tissue
GCP	Good Clinical Practice (Guidelines)
GSI	Gilead Sciences, Inc.
HBV	hepatitis B virus
HCV	hepatitis C virus
HBcAb	hepatitis B virus core antibody
HBsAb	hepatitis B virus surface antibody
HBsAg	hepatitis B virus surface antigen
HDACi	histone deacetylase inhibitors
hERG	human ether-à-go-go-related gene
HLA	Human Leucocyte Antigen
HLT	high level term
HLGT	high level group term
HMG-Coa	3-hydroxy-3-methylglutaryl-coenzyme
HPF	high-power field
HIV	human immunodeficiency virus
hr	Hour
hsCRP	High sensitivity C-Reactive Protein
ICH	International Conference on Harmonization
ICS	intracellular cytokine staining
IC50	50% inhibitory concentration
IEC	Institutional Ethics Committee
IFN	Interferon
IFN-α	interferon-alpha
IMP	Investigational Medicinal Product
IND	Investigational New Drug (Application)
IP-10	interferon γ–inducible protein-10
IRB	Institutional Review Board

ISGs	interferon-stimulated genes
IUD	intrauterine device
IU	international unit
CCI	[redacted]
Kg	Kilogram
LAM	Lactational amenorrhea method
LRA	latency reversal agent
LLN	lower limit of the normal range
LLOD	lower limit of detection
LLOQ	lower limit of quantitation
LLT	lower level term
LN	lymph node
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities; MedDRA®
mg	milligram
µg	microgram
µL	microliter
min	minute
mDC	conventional (myeloid) dendritic cell
mL	milliliter
mRNA	messenger ribonucleic acid
NDA	New Drug Application
NK	natural killer (cell)
NRTI	Nucleoside Reverse-Transcriptase Inhibitors
NOAEL	no observed adverse effect level
OAV	oral antivirals
PCR	Polymerase Chain Reaction
PEG	pegylated interferon
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamics(s)
pDC	plasmacytoid dendritic cell
PK	pharmacokinetic(s)
POC	Proof of concept
PrEP	Pre-Exposure Prophylaxis
PT	prothrombin time
PT	preferred term
pVL	plasma viral load
PXR	pregnane X receptor
Q1	First quartile
Q3	Third quartile
QD	*quaque die* (one- or once-a-day)
QOD	every other day (dosing)
qPCR	quantitative PCR

QVOA	Quantitative viral outgrowth Assay
RBC	red blood cell (count)
RNA	ribonucleic acid
sCD	Soluble CD
SAD	single ascending dose
SADR	serious adverse drug reaction
SAE	serious adverse event
SCA	single copy assay
SD	standard deviation
SEC	Safety Evaluation Committee
SIV	Simian immunodeficiency virus
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1/2	estimate of the terminal elimination half-life of the drug, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
Th1/Th2/Th17	T helper cells (1, 2, 17)
Tr1	Type 1 T regulatory cells
Tlast	time (observed time point) of C_{last}
Tmax	time (observed time point) of C_{max}
Treg	T regulatory (cells)
TBD	to be determined
TFV	tenofovir
TLR	toll-like receptor
ULN	upper limit of the normal range
US	United States
USA	United States of America
vs	versus
WHO	World Health Organization
wt	weight
λz	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the concentration of drug versus time curve

1. INTRODUCTION

1.1. Background

Human immunodeficiency virus type-1 (HIV-1) infection is a life-threatening and serious disease that is of major public health interest around the world. There are approximately 2.4 million people in North America and Western and Central Europe living with HIV-1 and 36 million people worldwide {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2016}. Untreated infection leads to deterioration in immune function and death. The availability of antiretroviral therapy (ART) has been associated with a dramatic decrease in acquired immune deficiency syndrome (AIDS)-related morbidity and mortality {Palella 1998}, {Mocroft 1998}, {Sterne 2005}.

While ART effectively suppresses HIV replication, HIV infection remains incurable. Persistent viral reservoirs fuel rebound viremia when treatment ceases. Despite the availability of chronic treatment, morbidity, and mortality due to HIV infection remain high due to the latent HIV reservoir, which may contribute to ongoing inflammation-driven disease. Current therapy is associated with challenges with tolerability, long-term adherence and safety, drug-drug interactions, and expense. Persistent HIV infection may also be associated with psychosocial stigma. Thus, the discovery and development of therapeutic interventions that can eradicate or control HIV reservoirs, leading to long-term ART-free remission or HIV cure, is a major priority.

Following entry into a target cell, HIV-1 stably integrates into the host genome, thus establishing the basis for latent infection and the main barrier to HIV cure. Neither the host immune system nor ART can eliminate transcriptionally inactive virus. Therefore, adjunctive therapies that efficiently reactivate ("kick") virus out of this latent reservoir to enable its destruction ("kill") may be required for viral eradication. This "kick and kill" strategy to cure or induce long-term HIV remission has been tested in clinical trials of latency reversal agents (LRA) such as histone deacetylase inhibitors (HDACi). While short-term treatment with HDACi such as romidepsin appears to be safe and may activate viral transcription in individuals virologically suppressed on ART, the size of the latent viral reservoir as measured by total peripheral blood mononuclear cell (PBMC)-associated HIV-1 DNA or quantitative viral outgrowth assay (QVOA) appears to be unchanged {Sogaard 2015}. However, a TLR9 agonist has been dosed in HIV-1 positive participants on ART in a single-arm open-label study demonstrating increases in plasma IFN-α levels, transcriptional (messenger ribonucleic acid [mRNA]) induction of interferon stimulated genes (ISGs), activation of pDCs, activation of cytotoxic natural killer (NK) and CD8+ T cells with transient increases in plasma HIV-1 RNA in a subset of individuals {Vibholm 2017}. It is postulated that a combination of therapies exerting viral latency reversing activity and engagement of the host immune system will be necessary to have a demonstrable effect on reducing the HIV-1 reservoir. To date there is no fully validated biomarker for the latent HIV-1 reservoir. Therefore, measurement of the time to viral rebound and/or new viral load set-points following analytical treatment interruption (ATI) is the most accurate endpoint to evaluate the efficacy of "kick and kill" interventions. The AIDS Clinical Trials Group (ACTG) has reported that ATI can be conducted safely in patients {Bar 2016, Li 2016} and that certain measures of the HIV reservoir may be correlated with time to viral rebound {Li 2016}.

While previous ATI trials have included standard cohorts of chronically HIV-infected participants, a subset of infected individuals known as HIV controllers offers a unique opportunity to evaluate novel HIV cure interventions. These patients are defined by a history of maintaining undetectable or low HIV viral loads in the absence of ART, with the mechanism of control likely being a robust adaptive immune response {Walker 2013}. However, while controllers may be able to suppress HIV replication without treatment for extended periods, recent evidence supports initiating ART to minimize the pathologic immune activation and inflammation associated with chronic HIV infection {Hatano 2013}. Therefore, studying "kick and kill" interventions in the setting of an ATI in treated HIV controllers could potentially provide useful information while minimizing the risk of high peak viral load rebound in the absence of ART.

GS-9620 is an orally-administered toll-like receptor (TLR) 7 agonist currently in clinical development for the treatment of HIV. In vitro, GS-9620 appears to mediate both HIV-1 "kick" and "kill" activity. In a rhesus macaque model of chronic SIV infection, treatment with GS-9620 or its close analog GS-436986 has also demonstrated the ability to both "kick" and "kill": treatment resulted in transient detection of plasma viremia within 24-72 hours of dosing, decreases in ex vivo SIV production from T-cell receptor stimulated PBMC cultures or immune cell isolates of peripheral lymph nodes comparing pre-treatment to post-dosing samples and a ~0.5 $\log_{10}$ lower viral load set-point after discontinuation of ART {Lim 2018}. Most importantly, in a subset of animals, there was a lack of detectable plasma virus (< 50 SIV RNA copies/mL) for at least 2 years after discontinuation of ART. During the off ART, phase two animals from one of the studies had no viral rebound after administration of antibodies depleting NK and CD8+ lymphocytes or transfer of viral infection after infusion of mononuclear immune cells from lymph node and peripheral blood into naïve animals; implying a substantial reduction in viral reservoir. The administration of multiple doses of GS-9620 has been shown to be safe in clinical studies of healthy subjects (single doses up to 12 mg), hepatitis B virus (HBV) infected subjects (multiple doses up to 4 mg), and subjects with chronic HIV-1-infection on ART (multiple doses up to 8 mg). This study will therefore investigate the safety and efficacy of GS-9620 in a cohort of HIV controllers on ART who undergo ATI following treatment with GS-9620.

1.2. GS-9620

1.2.1. General Information

GS-9620 is an orally-administered TLR7 agonist in development for the treatment of HIV infection.

Data in-vitro have shown that GS-9620 is a potent and selective TLR7 receptor agonist with a > 30-fold selectivity for TLR7 (32-fold based on EC_{50} and 81-fold based on minimum effective concentration) over toll-like receptor 8 (TLR8), with no detectable stimulation of other human TLRs at concentrations up to 100 μM (PC-243-2031).

Nonclinical data in mice and in chimpanzees chronically infected with HBV demonstrated that oral administration of GS-9620 induce a type I IFN dependent innate response in the liver, as measured by induction of interferon-stimulated genes (ISGs), in the absence of concomitant serum detectable levels of IFN-α (i.e. a pre-systemic response) {Fosdick 2013}, {Lanford 2013}. The induction of type I IFN-dependent innate immune responses without the induction of detectable systemic IFN-α has been confirmed in healthy human subjects (GS-US-320-0101) and patients affected by chronic hepatitis C (GS-US-243-0102) or by chronic hepatitis B (GS-US-283-0102, GS-US-283-0106, GS-US-283-1059, and GS-US-283-1062).

For further information on GS-9620, refer to the investigator's brochure for GS-9620.

1.2.2. Preclinical Pharmacology and Toxicology

Preclinical in vivo pharmacology studies in different non-human primate species have consistently demonstrated that GS-9620 induces IFN-α, multiple cytokines, chemokines, peripheral blood mononuclear cell (PBMC) derived ISG mRNAs and peripheral immune cell activation in a dose-dependent manner. Of note, with escalating doses of GS-9620 cynomolgus monkeys were shown to have an exaggerated IFN-α response both in vitro and in vivo compared to other species (mice, chimpanzees, and humans).

In in vitro PBMC cultures, GS-9620 stimulated markedly higher maximal levels of secreted IFN-α in cynomolgus monkey PBMC compared to human PBMC cultures; the in vitro mean peak IFN-α was 9105 pg/mL and 1552 pg/mL in cynomolgus monkey and human PBMCs, respectively.

Similarly, the mean peak IFN-α concentration in serum following a single oral dose in vivo was notably higher in cynomolgus monkeys than healthy human volunteers at an equivalent dose; at 0.5 mg/kg (human equivalent dose 9.6 mg) the mean peak of serum IFN-α was 4859 pg/mL in cynomolgus monkey versus 93.7 pg/mL in human healthy volunteers receiving 12 mg dose [study GS-US-243-0101] (human equivalent dose was calculated using a conversion factor of 0.32 for cynomolgus monkey and assuming a human body weight of 60 kg {U. S. Department of Health and Human Services (DHHS) 2005}).

Single oral doses of GS-9620 given in preclinical studies in cynomolgus monkeys (0.05 to 0.5 mg/kg; human equivalent dose 1 – 9.6 mg) and mice (0.3 mg/kg; human equivalent dose 1.4 mg) human equivalent dose was calculated using a conversion factor of 0.08 for mice and assuming a human body weight of 60 kg {U. S. Department of Health and Human Services (DHHS) 2005} have shown that GS-9620 can induce an innate immunity gene expression signature, e.g. up-regulation of interferon-stimulated genes (ISG) in the absence of detectable serum IFN-α concentrations. These observations are consistent with the concept of a pre-systemic response elicited by oral GS-9620.

Body temperature increases were noted in the cardiovascular/respiratory safety pharmacology study in cynomolgus monkeys (≥ 0.5 mg/kg) at C_{max} exposures that were approximately equivalent to the C_{max} at the highest dose tested in HBV infected patients (4 mg; study GS-US-283-0102). Increases in heart rate were observed concurrently with the increases in body temperature and with the peak of IFN-α levels. Of note, body temperature and heart rate increase were not seen at the 4-mg dose in the human clinical studies. Increases in body temperature and heart rate are well-described side effects of exogenous IFN- α administration in humans {Vial 1994} and in nonhuman primates {Kubicek 1958}, {Vial 1994} and may reflect the sequelae of elevated IFN-α in the cynomolgus monkeys.

In an in vitro electrophysiology assay GS-9620 inhibited the human ether-à-go-go-related gene (hERG)-mediated current at an IC_{50} (50% inhibitory concentration) value that was 150-fold higher than the C_{max} at the highest dose used in HBV infected patients (4 mg; study GS-US-283-0102). These margins are likely even higher once adjusted for protein binding.

No adverse cardiovascular effects were noted in cynomolgus monkeys at C_{max} exposures up to 5-fold higher than the projected C_{max} (4.19 ng/mL) for an 8 mg dose of GS-9620. No notable effects on the central nervous or respiratory systems were seen in the safety pharmacology studies. Safety pharmacology studies did not identify any major effects that would impede the use of GS-9620 in human subjects.

Preclinical toxicology studies were conducted in single dose and multiple dose settings in different animal species.

Single Dose Toxicology Studies

Single oral doses of GS-9620 were well tolerated at up to 30 mg/kg and up to 2 mg/kg in mice and cynomolgus monkeys, respectively. At higher doses, mortality was noted in single dose oral studies in mice at 100 mg/kg (TX-243-2008) or greater (AD-243-2017) and in a single woodchuck administered 10 mg/kg orally (AD-243-2014). Additionally, mortality was observed following intravenous administration of 3 mg/kg to rhesus monkeys (AD-243-2034). These deaths were attributed to high systemic exposure to GS-9620 (≥ 21-fold higher than the AUC_{0-24} in HBV infected patients [study GS-US-283-0102]; 44.3 pg•h/mL at 4 mg).

Multiple Dose Toxicology Studies

Oral administration of GS-9620 every-other-day (QOD) was well tolerated in the 4-week and 6-week studies in mice, with the highest doses of 5 and 3 mg/kg QOD, respectively, being the no observed adverse effect levels (NOAELs) (Table 1-1).

In cynomolgus monkeys, GS-9620 was well tolerated in the 4-week study with the highest dose of 1.5 mg/kg QOD being the NOAEL (Table 1-1).

In the 26-week cynomolgus monkey toxicity study, GS-9620 administration at ≤ 0.15 mg/kg/dose was well tolerated. Administration of 0.50 mg/kg every other day (reduced to 0.3 mg/kg every other day at Week 11) resulted in morbidity/mortality of 3 animals beyond 8 weeks of QOD dosing. In this study the pharmacodynamic effects appeared to increase over time and were associated with high levels of circulating IFN-α. Cynomolgus monkeys were the most sensitive toxicology species and have an apparent exaggerated IFN-α response to GS-9620 (Table 1-1). The observed mortalities in cynomolgus monkeys are consistent with data obtained from the New Drug Application (NDA) approvals of peginterferon alpha 2a (Pegasys®) and peginterferon alpha 2b (Peg-Intron®) showing that repeated high doses of IFN-α or PEG cause a similar spectrum of effects in cynomolgus monkeys as those observed in the 26-week toxicology study with GS-9620 {European Medicines Agency (EMA) 2006}, {Pilaro 2000}. The margins of exposure in the preclinical species, based on IFN-α stimulation, range from 0.33 to 122-fold depending on the duration of exposure due to GS-9620 dosing every other day. Less frequent administration, once every other week, in the clinical setting would be expected to minimize chronic IFN-α exposure side effects.

Table 1-1. Estimated Margins of GS-9620 Following Oral Administration at the Highest Anticipated Human Dose

Species	Duration	Dose (mg/kg/dose)	$AUC_{0\text{-}tau}$[a] ng•h/mL	C_{max}[a] ng/mL	Mean Peak IFN-α pg/mL	Margin of Exposure		
						AUC_{inf}[b]	C_{max}[b]	IFN-α[c]
Mouse	QOD x 4 weeks	5 (NOAEL)	43.5	13.4	237	0.3x	1.1x	2.4x
	QOD x 26 weeks	3 (NOAEL)	15.8	6.64	60.7	0.1x	0.6x	0.6x
Cynomolgus Monkey	QOD x 4 weeks	1.5 (NOAEL)	73.8	86.7	11900	0.5x	7.2x	122x
	QOD x 26 weeks	0.15 (NOAEL)	0.171	0.077	32	0.001x	0.006x	0.33x
		0.5/0.3	1.82[d]	0.504[d]	23085[d]	0.013x	0.04x	21x

a Males and females combined, Week 4 or Week 26 as applicable
b Margins of exposure were calculated using clinical GS-9620 C_{max} and AUC_{inf} at 12 mg of 12.0 ng/mL and 140 ng•h/mL, respectively (GS-US-243-0101)
c Margins of exposure were calculated using the mean peak for IFN-α (97.3 pg/mL) from healthy subjects dosed with 12 mg GS-9620 (GS-US-243-0101)
d Week 17 at 0.3 mg/kg
Source: Studies TX-243-2005, TX-243-2011, TX-243-2004, TX-243-2012

Monotherapy Proof-of-Concept Studies in Monkeys

In a rhesus macaque model of chronic SIV infection, treatment with GS-9620 or its close analog GS-436986 has also demonstrated the ability to both "kick" and "kill." Treatment resulted in transient detection of plasma viremia within 24-72 hours of dosing, decreases in ex vivo SIV production from T-cell receptor stimulated PBMC cultures or immune cell isolates of peripheral lymph nodes comparing pre-treatment to post-dosing samples and a ~0.5 $\log_{10}$ lower viral load set-point after discontinuation of ART {Lim 2018}. Most importantly, in a subset of animals, there was a lack of detectable plasma virus (< 50 SIV RNA copies/mL) for > 2 years after discontinuation of ART. During the off ART phase, two animals from one of the studies had no viral rebound after administration of antibodies depleting NK and CD8+ lymphocytes or transfer of viral infection after infusion of mononuclear immune cells from lymph node and peripheral blood into naïve animals; implying a substantial reduction in viral reservoir.

1.2.3. Clinical Trials of GS-9620

As of 27 March 2018, 4 Phase 1 clinical studies, 1 Phase 2 clinical study, and 1 registry study have been completed in which 55 healthy subjects, 42 HCV infected subjects, and 230 subjects with chronic hepatitis B (CHB) (189 virologically suppressed and 41 treatment naive subjects) were dosed with GS-9620. In addition, a Phase 2 clinical trial (283-1059) in virologically suppressed CHB subjects has completed dosing and a Phase 1 clinical trial (382-1450) in HIV-1-infected subjects on ART is currently on-going. In these studies, single doses ranged from 0.3 mg to 12 mg in healthy volunteers, and from 0.3 mg to 4 mg in HCV- and HBV-infected subjects. Multiple doses (two doses one week apart and up to 12 doses one week apart) were assessed in HCV-infected and HBV-infected subjects and ranged from 0.3 mg to 4 mg.

In HIV-infected subjects, multiple doses of GS-9620 ranging from 1 mg to 6 mg were assessed, with the 8 mg dosing cohort currently in progress.

1.2.3.1. GS-US-243-0101

Study GS-US-243-0101 was a first-in-human, randomized, double-blind, placebo-controlled, single ascending dose (SAD) study of GS-9620 in 75 healthy male and female subjects. The primary objective of the study was to evaluate the safety and tolerability of GS-9620 and the secondary objectives were to characterize the plasma PK/PD profile of GS-9620. Doses used were: 0.3, 1, 2, 4, 6, 8, and 12 mg.

The treatment was generally well tolerated. There were no Grade 4 AEs or serious adverse events (SAEs) reported, and most AEs were mild. No individual subject discontinued due to AEs or laboratory abnormalities. Treatment-emergent Grade 3 AEs included pyrexia in 2 subjects who received GS-9620 12 mg. A higher incidence of flu-like symptoms was also reported in subjects administered the higher doses (8 and 12 mg).

Plasma concentrations of GS-9620 peaked between 1.5 and 6 hours after dosing and declined gradually over 48 hours. The mean maximum plasma concentration (C_{max}) ranged from 184.2 pg/mL at the 0.3 mg dose to 11.97 ng/mL at the 12 mg dose. Exposures were higher in the fasted state than in the fed state. After the 1 mg, 2 mg, and 4 mg doses, GS-9620 was detectable at 48 hours after dosing and had a median terminal half-life between 17.16 and 26.96 hours.

Three ISGs were analyzed: ISG15, MX-1 and OAS-1. Significant ISG induction was observed at the 2-mg dose and above. ISG15 mRNA expression showed the highest induction compared to MX-1 and OAS-1. Serum IFN-α was detected only in subjects who received the 8 or 12 mg doses. A dose-dependent induction was observed for serum IP-10 but not for TNF-α. Dose-dependent T cell activation was also observed at the 2 mg dose and above.

In summary, single doses of GS-9620 up to 12 mg were well tolerated, with significant ISG induction at doses of 2, 4, and 6 mg in the absence of detectable serum IFN-α or systemic AEs.

1.2.3.2. Other Phase 1 studies

The following studies have also demonstrated good tolerability of GS-9620 (see IB for details):

- GS-US-243-0102: A Phase 1b ascending, single and multiple-dose study evaluating the safety, PK, PD, and antiviral activity in treatment-naive HCV subjects.
- GS-US-283-0102: A Phase 1b ascending, single and multiple-dose study evaluating the safety, PK/PD, and antiviral activity in virologically-suppressed HBV subjects.
- GS-US-283-0106: A Phase 1b ascending, single and multiple-dose study evaluating the safety, PK/PD, and antiviral activity in treatment-naive HBV subjects.
- GS-US-283-0110: An observational registry study of subjects who did not achieve loss of HBsAg and sustained HBV viral load reduction below the level of quantitation in Gilead-Sponsored trials of GS-9620 in subjects with chronic HBV infection.

1.2.3.3. GS-US-283-1059

GS-US-283-1059 was a Phase 2, randomized, double-blind, placebo-controlled multi-center study to evaluate the safety and efficacy of GS-9620 in HBV-infected subjects who are virologically suppressed. In this study, 162 subjects received weekly dosing with GS-9620 (1, 2 or 4 mg) or placebo for a total of 4 (Cohort A), 8 (Cohort B) or 12 (Cohort C) weeks. The efficacy of GS-9620 was evaluated by assessing the change from baseline to Week 24 in HBsAg levels.

Overall, once-weekly dosing of GS-9620 1, 2, or 4 mg for 4, 8, or 12 weeks was generally well tolerated in virologically-suppressed subjects with CHB on OAV. Most subjects had Grade 1 (mild) AEs and, except for the Cohort C 4-mg group in which a higher proportion of subjects had Grade 2 (moderate) and 3 (severe) AEs compared with Cohorts A and B. No other dose-related or treatment duration-related safety findings were observed. No Grade 4 (life threatening) AEs were reported in any of the cohorts. Four subjects had SAEs, 3 of these subjects had AEs that led to discontinuation of study drug, and 3 of the 4 subjects had study drug interrupted due to AEs. No deaths occurred in any study participant.

Two subjects interrupted study treatment after having experienced SAEs due to an overdose caused by a dispensing error at the study site. One of these subjects randomized to 2 mg GS-9620 mistakenly received 10 mg and one subject randomized to 4mg mistakenly received 20 mg. These 2 subjects experienced transient Grade 3 AEs of flu-like symptoms and decline in lymphocytes count. The subject who received 10 mg experienced Grade 3 AEs of pyrexia, chills and hot flush, all SAEs that were assessed as related to study drug by the investigator. The subject who received 20 mg experienced SAEs of Grade 3 AE of tremor and Grade 2 hypotension requiring hospitalization. This subject also experienced additional Grade 2 AEs of abdominal pain, diarrhea, and vomiting, and an increase in ALT value. For both subjects, each of the AEs resolved within 24 hours after overdose. A meeting of the Data Monitoring Committee reviewed these events and determined them to be due to the overdose of GS-9620 with expected effects of interferon-alpha induction and cytokine release and allowed for the study to proceed as planned. The other two subjects with SAEs were in Cohort C (cataract, which was reported in one subject with a medical history of cataract, and cholecystitis, which was reported in the other subject). The subject who experienced cholecystitis also withdrew from study drug and the study.

Most AEs reported were Grade 1 or Grade 2 in severity. No Grade 4 (life threatening) AEs occurred in any of the cohorts. For Cohort A, 1 subject in each group had Grade 3 AEs. None of the Grade 3 AEs led to withdrawal from study drug and none occurred in more than 1 subject. All of the Grade 3 AEs resolved. Excluding the 2 overdosed subjects discussed above, 2 subjects (placebo and GS-9620 1 mg) experienced transient Grade 3 AE of anxiety and diarrhea, respectively, during the treatment period with GS-9620/placebo; both AEs resolved within 24 hours. For Cohort B, no subjects had Grade 3 AEs. For Cohort C, 6 subjects had Grade 3 AEs: 2 subjects in the GS-9620 1-mg group, 1 subject in the GS-9620 2-mg group, 2 subjects in the GS-9620 4-mg group, and 1 subject in the placebo group. Two subjects, both in the GS-9620 4-mg group, with Grade 3 AEs (cholecystitis [discussed above] and panic attack) withdrew from the study and study drug.

Overall, patients from both the GS-9620-treated and placebo groups experienced a similar number of treatment emergent AEs (TEAEs) (68% study drug vs. 70% placebo). Upon assessment of relation to study drug, 37% of patients treated with GS-9620 reported at least one AE compared to 50% of placebo patients, all of which were mild to moderate in severity. No dose-dependency for AEs was observed across cohorts. The most commonly reported related AEs (for ≥2 or more patients) in Cohort A were fatigue (4 of 16 [25.0%] subjects) and diarrhea, headache, oropharyngeal pain, pruritus, and pyrexia (each of which occurred in 2 of 16 patients [12.5%]) (1-mg group); headache (4 of 15 [26.7%] subjects), fatigue (3 of 15 [20.0%] patients) and chills (2 of 15 [13.3%] patients) (2-mg group); and fatigue and pyrexia (each in 3 of 16 [18.8%] patients) and headache (2 of 16 [12.5%] patients) (4-mg group). In Cohort B, headache (6 of 18 [33.3%] patients), nausea (3 of 18 [16.7%] patients) and acne, dizziness, fatigue, insomnia, and oropharyngeal pain (each in 2 of 18 [11.1%] patients) (1-mg group); headache and dizziness (each in 2 of 17 [11.8%] patients) (2-mg group); and headache (4 of 17 [23.5%] patients) and fatigue, influenza-like illness, and rhinorrhea (each in 2 of 17 [11.8%] patients) (4-mg group) were most common. In Cohort C, headache, fatigue, influenza-like illness (each in 4 of 16 [25.0%] patients) and asthenia, pyrexia and somnolence (each in 2 of 16 [12.5%]

patients) (1-mg group); abdominal pain upper and headache (each in 3 of 17 [17.6%] patients) and fatigue (2 of 17 [11.8%] patients) (2-mg group); and asthenia (5 of 14 [35.7%] patients), headache, influenza-like illness, and pyrexia (each in 3 of 14 [21.4%] patients) and myalgia (2 of 14 [14.3%] patients) (4-mg group). Headache was the most commonly reported placebo group AE (40-50% of patients).

Among the patients dosed with GS-9620, treatment-emergent graded ALT elevations were seen in 5 subjects (4 subjects with Grade 1 and one subject with Grade 2). All grade 1 elevations were transient (1 placebo, 1 GS-9620 2 mg, and 2 GS-9620 4 mg) and the grade 2 elevation occurred 22 days after the last dose of GS-9620 4 mg and reduced to grade 1 elevation 3 days later.

Please refer to the current GS-9620 Investigator's Brochure for the treatment of chronic hepatitis B virus infection for additional information regarding the above studies.

1.2.3.4. GS-US-283-1062

This Phase 2, randomized, double-blind, placebo-controlled study was conducted to evaluate the safety and efficacy of administering either 1 mg, 2 mg or 4 mg of GS-9620 orally once a week (every 7 days) for 12 doses (Weeks 0-11) in adult subjects with CHB who were not currently on treatment for CHB. 192 subjects were randomized in a 1:2:2:2 ratio to 1 of the 4 treatment arms (placebo, GS-9620 1 mg, 2 mg, or 4 mg) for weekly dosing for a total of 12 doses and stratified by HBeAg status (positive versus negative) and ALT (> versus ≤ 19 IU/mL for female; > versus ≤ 30 IU/mL for male). All subjects were also treated with TDF 300 mg oral daily for 48 weeks.

Preliminary interim safety results from Week 48 show that overall, once-weekly dosing of GS-9620 1, 2, or 4 mg was generally well tolerated. 65% of subjects overall had at least 1 AE during the study and most of the reported AEs were Grade 1 (mild) or 2 (moderate) in severity. Overall, the majority of subjects had Grade 1 (mild) or moderate (Grade 2) AEs. Six subjects experienced Grade 3 (severe) AEs. No Grade 4 (life threatening) AEs were reported in any of the treatment groups.

Four subjects had treatment-emergent SAEs: an SAE of laceration (deep laceration on the right foot) on Day 133 which resolved on Day 252, an SAE of asthma (worsening of asthma) on Day 257 which resolved on Day 288, an SAE of breast cancer on Day 422 continuing at the time of the interim data cut, and an SAE of abdominal pain (exacerbation of chronic generalized abdominal pain) on Day 71 which resolved on Day 85. All SAEs were considered by the investigator to be unrelated to study drugs or to study procedures. No action was taken with study drugs, with the exception of TDF dose interruption for the abdominal pain case and dose withdrawn for the breast cancer case. No deaths occurred.

Six subjects overall (3.1%) discontinued study drug due to an AE, all of which were considered related to study drugs by the investigator.

Across the treatment groups, most laboratory abnormalities were Grade 1 or 2 in severity. Five subjects had ALT ≥ 10x ULN and thirty had ALT between 3x ULN and < 10x ULN and > 2x nadir.

1.2.3.5. GS-US-382-1450

GS-US-382-1450 is a Phase 1b, single/multiple ascending dose, randomized, double-blind, placebo-controlled multi-center study to evaluate the safety of GS-9620 in HIV-infected subjects who are virologically suppressed. In this study, approximately 32 subjects received biweekly dosing with GS-9620 (1, 2 or 4 mg) or placebo for a total of 6 doses, or 6 mg for a total of 10 doses. The 1 mg, 2 mg, 4 mg and 6 mg dosing cohorts have now completed dosing. Enrollment of the 8 mg cohort is complete and dosing is ongoing.

In the 1 mg dose cohort (Cohort 1) a total of 8 subjects were enrolled. There were no deaths, SAEs, Grade 3 or 4 AEs or AEs leading to discontinuation. There were no study drug-related AEs. 6 subjects experienced a treatment-emergent AE. These included fatigue (4), nasal congestion (3), cough (2), oropharyngeal pain (2), and nausea (2). There were no Grade 3 or 4 lab abnormalities. There was one case of post-dose increase in plasma HIV-1 RNA that failed to resolve to <50 copies/mL within 10 days. In this subject the HIV-1 RNA rose to 1040 copies/mL at day 7 post-dose 3, was 629 copies/mL at day 10 and returned to undetectable at day 17. There were no other significant lab changes and the only concomitant AE was “vessel site puncture pain”. The safety evaluation committee (SEC) recommended proceeding with enrollment of Cohort 2.

In the 2 mg dose cohort (Cohort 2) a total of 8 subjects were enrolled. There was one loss to follow-up after dose 2, no deaths and no AEs leading to discontinuation. There was one SAE (diverticulitis considered unrelated to study drug) and 1 Grade 3 or 4 AE. There was one drug-related AE of headache. There were no treatment-emergent AEs occurring in 2 or more subjects. There were no Grade 3 or 4 lab abnormalities and no dose-limiting toxicities. The SEC recommended proceeding with Cohort 3 (4 mg), which is now complete.

In the 4 mg dose cohort (Cohort 3) a total of 8 subjects were enrolled. There were no AEs leading to study drug discontinuation, no Grade 3 or 4 AEs and no SAEs. One subject experienced AEs of sluggishness and dysgeusia which were considered related to study drug by the investigator. Six subjects experienced treatment-emergent laboratory abnormalities, all of which were Grade 1 or 2.

In the 6 mg dose cohort (Cohort 4) of this study, 6 subjects experienced treatment-emergent AEs. Three of these subjects had AEs which were considered to be related to study drug by the investigator: one subject had decreased concentration, vivid dreams, sweats, and fatigue; another subject had headache and increased peripheral neuropathy; the third subject had fatigue, myalgia, and nasal congestion. All of these AEs were grade 1 or 2 and all resolved during the dosing period. There have been no grade 3 or 4 AEs, AEs leading to study drug discontinuation, SAEs, or deaths. The protocol-defined SEC reviewed blinded safety data from the 6 mg cohort on 25 September 2017 and recommended proceeding with the addition of the 8 mg cohort (Cohort 5).

In the 8 mg dose cohort (Cohort 5) of this study, a total of 8 subjects have been enrolled and are currently being dosed with study drug. At the time of the interim safety data cut (30 April 2018), all subjects have completed 5 out of 10 doses, and 3 subjects have completed 6 doses. There have been no grade 3 or 4 AEs, AEs leading to study drug discontinuation, SAEs, or deaths. Three subjects have had mild AEs considered related to study drug by the investigator. These AEs include chills and malaise in one subject, pyrexia and myalgia in another subject, and headache in the last subject. All AEs resolved within one day and have not recurred after Dose 3, thus far.

1.3. Rationale for This Study

Despite the extensive advances made in the treatment of chronic HIV-1 infection, control and/or eradication of the latent HIV-1 reservoir is still needed to achieve a remission or cure that abrogates the requirement for lifelong ART. To this end, "kick and kill" strategies to reactivate and target latent virus have been tested in a number of clinical trials, but none have resulted in lasting virologic remission. GS-9620 is a promising candidate for this approach given the demonstration of both SIV reactivation (as measured by transient plasma viremia in the presence of ART), decrease in SIV reservoir (as measured by proviral DNA in PBMCs, lymph node and colon), and ~0.5 log reduction in SIV set point relative to pre-ART plasma viral load set point following ART interruption in studies of SIV-infected rhesus macaques treated with GS-436986, a close analog of GS-9620. In a second study in SIV-infected rhesus on ART the TLR7 agonists GS-9620 or GS-436986 administered for 10 or 19 doses produced transient plasma viremia within 24-72 hours after dosing. Sampling PBMCs and immune cell isolates from lymph node biopsies prior to TLR7 agonist administration and after completing all doses demonstrated a decrease in the amount of SIV production following T-cell receptor stimulation. Interestingly, two of these animals, one from the GS-9620 dosing group and one from the GS-436986 dosing group had no detectable ex vivo SIV production from both PBMCs and isolated immune cells from lymph node biopsies. Most importantly, after ART discontinuation these same two animals had no detectable plasma virus (< 50 SIV RNA copies/mL) rebound which has been sustained for at least twelve months. These results suggest the possible use of TLR7 agonists in combination with ART toward reduction of HIV reservoirs and ultimately finite therapies for HIV-1 infection. In addition, GS-9620 appears to be safe in healthy, HBV-infected, and HIV-infected subjects on ART.

The next goal is to measure the efficacy of GS-9620 in reducing and/or controlling the HIV-1 reservoir. Measurement of the time to viral rebound and/or new viral set-point following ATI is the most definitive method for evaluating HIV-1 cure interventions. The ACTG and other groups have demonstrated the safety of ATI in chronically HIV-infected individuals, despite the risk associated with viral rebound to high levels. Recent evidence supporting the initiation of ART in HIV-1 controllers (individuals defined as having a history of maintaining low plasma HIV-1 RNA copies/mL prior to ART) has resulted in the establishment of limited cohorts of treated controllers. Therefore, studying "kick and kill" interventions in the setting of an ATI in these subjects could potentially provide useful information while minimizing the risk of high peak viral load rebound in the absence of ART. The ability to delay plasma viral rebound and/or decrease viral load set point to less than pre-ART levels would suggest potential clinical benefit of GS-9620 in HIV-1-infected individuals for the first time.

The primary objective of study GS-US-382-3961 is to evaluate the safety and tolerability of a 10-dose regimen of GS-9620 in HIV-1 infected controllers on antiretroviral treatment (ART) and during analytical treatment interruption (ATI) following GS-9620 dosing. Secondary objectives include assessing virologic effects (HIV-1 reactivation, reservoir reduction, plasma viral load during ATI), pharmacokinetics, pharmacodynamics (cytokines and ISG), and immunologic effects (immune cell profile, function and inflammation).

1.4. Rationale for Dose Selection/Dosing Interval

An adaptive dose selection is being utilized in this study. The current dose of 8 mg is selected based on the safety and tolerability results from the ongoing blinded study GS-US-382-1450 in HIV-infected ART suppressed subjects. In the GS-US-382-1450 study, multiple doses of 1 mg, 2 mg, 4 mg and 6 mg every other week have been well-tolerated. A cohort of subjects receiving 8 mg or placebo every other week for 10 doses is ongoing, with all 8 subjects having received 5 out of 10 doses at the time of an interim safety data cut on April 30th, 2018. This dose level was deemed safe by the SEC on June 4, 2018, with no dose-limiting toxicities, no grade 3 or 4 AEs, no AEs leading to study drug discontinuation, no SAEs, or deaths.

Initial doses of GS-9620 have been selected based on the results from the study in healthy volunteers (GS-US-243-0101) that showed a dose dependent ISG mRNA induction from 0.3 mg up to 12 mg, with detectable serum IFN-α levels (lower limit of detection (LLOD) 15.6 pg/mL) only at the highest dose of 8 and 12 mg.

Initial dose selection was also supported by the results from studies in 50 HCV and in 100 HBV infected patients, in which doses up to 4 mg of GS-9620 were evaluated, either as a single dose or two doses one week apart. Safety data from these studies demonstrated that GS-9620 at doses up to 4 mg are well-tolerated with no evidence of dose dependent adverse events or laboratory abnormalities that are consistent with systemic immune activation such as flu-like symptoms, hematologic reductions or increases in liver enzymes including transaminases. In the majority of patients there was no detectable IFN-α in serum, consistent with the mechanism of action of pre-systemic innate immune system activation in the GALT and/or in the liver. Evidence of biological activity was observed in a dose dependent manner in all 3 studies, with maximal induction of ISG15 occurring within 48 hours and return to baseline levels of expression within 168 hours (7 days). In addition, the safety of a weekly dosing interval was supported by the observed elimination half-life (median range ~ 8 to 25 hours for 1, 2, or 4 mg doses in HBV- or HCV-infected subjects) and that no accumulation of GS-9620 occurred following once-weekly dosing.

A dosing schedule of once every 2 weeks is planned for this protocol in order to verify the resolution of GS-9620-induced viremia (>5000 copies/mL) prior to additional dosing. This schedule is more conservative than the weekly administrations used in the Phase 1 evaluations across the above-referenced studies in chronic hepatitis B and C patients. GS-9620 will be administered under fasted conditions to ensure maximal absorption.

1.5. Rationale for Biomarker Testing

It is hypothesized that the mechanism of action of GS-9620 is partly due to the initial activation of innate immunity via TLR7 positive pDCs, promoting the maturation of the pDCs and the release of antiviral cytokines and chemokines including IFN-α. The matured pDCs present HIV antigens to HIV-specific CD4 and CD8 T cells, thereby enhancing the HIV-specific adaptive response (cytotoxic CD8 T cells). In addition, the release of IFN-α could lead to activation of NK cells, and to activation of innate immunity. These multifaceted effector mechanisms (cytotoxic CD8 T cells, NK cells and antiviral cytokines) together strengthen the anti-HIV immune response and may lead to lowering the viral set point.

To provide proof of concept on the mechanism of action of GS-9620 in HIV-1 infected patients, several immunological biomarkers will be examined and are listed below. The testing outlined below is based upon the current state of scientific knowledge. CCI [redacted] Some or all of the following samples and biomarkers will be examined, depending on number of viable cells and blood volume obtained:

- Whole blood samples will be collected for interferon stimulated gene (ISG) mRNA measurements
- Whole blood samples, CCI [redacted]
- Whole blood samples, CCI [redacted]
- Levels of cytokines/chemokines CCI [redacted] will be quantified by immunoassays.

[redacted]

1.6. Risk/Benefit Assessment for the Study

Potential risks associated with GS-9620 include transient flu-like symptoms (such as chills, pyrexia, aches and headache) and transient increases in plasma HIV-1 viral load that are expected to resolve by the end of the dosing period. Potential risks of ATI include rebound of plasma HIV-1 viremia to >50 copies/mL, development of HIV-1 resistance mutations, decrease in CD4+ T cell count, symptoms of retroviral syndrome and transmission of virus to other individuals.

To mitigate these risks, plasma viral load and CD4+ T cell count will be measured frequently during ATI and ART will be promptly reinitiated according to the protocol-defined algorithm. Subjects will also be monitored for adverse events, and ART will be reinitiated if these are judged (by the investigator and/or sponsor) to be related to the ATI. In addition, subjects will be required to agree to the use of barrier prophylaxis for the duration of the study. The initial selection of subjects who have a history of a low pre-ART viral set point ≤5000 copies/mL and the availability of a fully active alternative ART regimen, in the event of discontinuation of the current ART regimen with development of resistance, will further minimize the risks of ATI.

Potential benefits include reduction of the latent HIV-1 viral reservoir, enhanced immune control of virus producing cells, and finally the combination of these effects on HIV-1 viral control (measured as plasma virus rebound and viral load set point) in the absence of ART. There are no direct benefits to subjects participating in this study.

1.7. 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 safety and tolerability of a 10-dose regimen of GS-9620 in HIV-1 infected controllers on antiretroviral treatment (ART) and during analytical treatment interruption (ATI) following GS-9620 dosing

The secondary objectives of this study are:

Virology

- To evaluate the effect of GS-9620 in reactivating the HIV-1 reservoir, as measured by changes in plasma HIV-1 RNA by Taqman 2.0
- To evaluate the effect of GS-9620 in modulating time to virologic rebound and plasma viral set-point following ATI

Immunology/Pharmacodynamics

- To evaluate the pharmacodynamics (PD) of GS-9620 as measured by changes in serum/plasma cytokines, and mRNA of interferon-stimulated genes (ISGs) in whole blood
- To evaluate effects of GS-9620 on immune cell activation in whole blood

Pharmacokinetics

- To evaluate the plasma pharmacokinetics (PK) of GS-9620

CCI [redacted]

3. STUDY DESIGN

3.1. Endpoints

The primary endpoint of this study is:

- Incidence of treatment-emergent SAEs and all treatment-emergent adverse events

The secondary endpoints of this study are:

Virology

- Changes in plasma HIV-1 RNA by Taqman 2.0
- Time to virologic rebound and change in plasma viral set-point following ATI
- Peak HIV-1 viral load during ATI

Immunology/Pharmacodynamics

- Changes in serum/plasma cytokines, and mRNA of ISGs in whole blood
- Changes in immune cell activation in whole blood

Pharmacokinetics

- PK parameters of GS-9620 in plasma

CCI

[redacted]

[redacted]

3.2. Study Design

This is a randomized, double-blind, two period, single cohort study involving HIV-1 infected controllers on ART with a history of pre-ART plasma HIV-1 RNA between 50 and ≤5000 copies/mL.

The study will be conducted in three periods. In Period 1, up to 30 subjects will be randomized 2:1 to receive GS-9620 or placebo-to-match. All subjects will receive up to 10 doses of their assigned study treatment administered orally every 14 days. Subjects will continue to take their prescribed ART during Period 1.

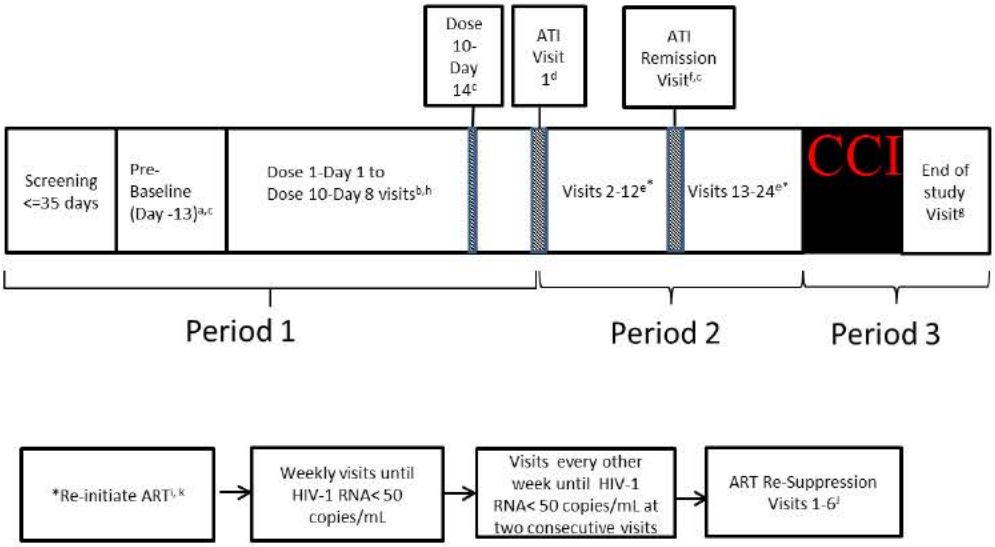
In Period 2, all subjects will discontinue ART and be monitored for rebound in HIV-1 plasma viremia.

In Period 3[redacted]

[redacted]

B) If subjects restart ART at the start of Period 3, subjects will complete ART Re-Initiation Visits, and then Post ART Re-Suppression Visits monthly for 6 additional months (Post ART Re-Suppression Visits 1-6). For these subjects, the last study visit will be the Post ART Re-Suppression Visit 6.

Figure 3-1. Study Schema



a Subjects will be randomized at Pre-Baseline/Day -13

b Subject dosing to occur every 14 days on Dose 1-Day 1, Dose 2-Day 1, Dose 3-Day 1, Dose 4-Day 1, Dose 5-Day 1, Dose 6-Day 1, Dose 7-Day 1, Dose 8-Day 1, Dose 9-Day 1 and Dose 10-Day 1. Subjects to be monitored on Dose 1-Days 2 and 8, Dose 2-Day 8, Dose 3-Day 8, Dose 4-Days 2,4 and 8, Dose 5-Day 8, Dose 6-Day 8, Dose 7-Day 8, Dose 9-Day 8, Dose 10-Days 2,4, 8 and 14.

[redacted]

d ATI Visit 1 to occur at Dose 10-Day 28 for subjects with HIV-1 RNA <50 copies/mL at Dose 10-Day 14 visit. Subjects to discontinue ART from ATI Visit 1 through ATI Visit 24 CCI [redacted]. For subjects with viral load >50 copies/mL at Dose 10-Day 14, the ATI Visit 1 will only occur if undetectable viral load is achieved within two re-test measurements.

e Weekly visits 2-24

f ATI Remission Visit will be planned after completion of 12 weeks of ATI for subjects with plasma HIV-1 RNA <50 copies/mL in the absence of ART re initiation. If subjects have HIV-1 viral load <50 copies/mL at ATI Visit 12, the visit should occur within a week of ATI Visit 12. However, if the subject does not have HIV-1 viral load <50 copies/mL at ATI Visit 12, CCI [redacted]

g End of study visit may occur for subjects who have not re-initiated ART through Period 2 and 3

h If HIV-1 RNA viral load is >5000 copies/mL at any visit post Dose, viral load will be observed at next scheduled visit or retested within 4 days. The next dose will be withheld and only given if a viral load of ≤5000 copies/mL is achieved. The study procedure schedule will be reset relative to the next dose of GS-9620.

i During 24-week ATI period CCI [redacted], ART will be re initiated if any of the criteria below are met:

- if HIV-1 RNA is >10,000 copies/mL on four consecutive weekly measurements OR
- if HIV-1 RNA does not decrease to <1,000 copies/mL within 6 weeks of virologic rebound OR
- if CD4+ cell count is confirmed to decrease by >30% from pre ATI levels OR
- if CD4+ cell count is confirmed <350 cells/μL OR
- Per Investigator or Sponsor's discretion due to other clinical criteria

j ART may also be re-initiated during ATI period per investigator or sponsor discretion due to other clinical criteria

k Visits to occur monthly

l If subjects restart ART at the start of Period 3, subjects will go straight into ART Re-Initiation Visits, and then Post ART Re-Suppression Visits monthly for 6 additional months (Post ART Re-Suppression Visits 1-6).

[redacted]

3.3. Study Treatments

Subjects will be randomized in a 2:1 ratio to receive GS-9620 or Placebo-to-match. All subjects will receive up to 10 doses of their assigned study treatment administered orally every 14 days. Subjects will continue their prescribed ART regimen during treatment phase (Period 1).

Single cohort (n=30): GS-9620 8 mg or Placebo-to-match .

3.4. Duration of Treatment

Subjects will receive up to 10 doses of GS-9620 or placebo-to-match over a minimum of a 20- week period (Period 1), followed by 24 weeks of close observation post ATI start (Period 2), and additional follow up visits in Period 3 (either ART Re-Initiation Visits with Post ART Re-Suppression Visits CCI [redacted]), and an End of Study Visit, if applicable.

For subjects who re-initiate ART during first 24 weeks of ATI, duration of study will extend for 6 months following virologic re-suppression on ART (Post ART Re-suppression Visits 1-6).

After 24 weeks of ATI, subjects may either restart ART or remain off ART. Subjects who restart ART will complete ART Re-Initiation Visits and then will complete Post ART Re-Suppression Visits monthly for 6 additional months. For these subjects, the last study visit will be Post ART Re-Suppression Visit 6. CCI [redacted]

The End of study visit may occur for subjects who have not re initiated ART through Period 2 and 3.

3.5. Discontinuation Criteria

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.
- Unacceptable toxicity, 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 receives GS-9620 and experiences one or more DLTs (at discretion of SEC)
- Subject requests to discontinue for any reason
- Subject noncompliance
- Pregnancy during the study; refer to Appendix 5
- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC)

3.6. End of Study

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

3.7. 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.

3.8. Source Data

Source data will be collected using the system established by the Investigator.

3.9. Biomarker Testing

3.9.1. Biomarker Samples to Address the Study Objectives

Biological specimens will be collected in this study as described in Section 6. The specimens will be used to evaluate the association of exploratory, systemic and/or tissue specific biomarkers with the study drug response, including efficacy and/or adverse events and to increase knowledge and understanding of the biology of HIV and related diseases and/or the validation of a companion diagnostic for HIV cure. The specific biomarkers will include, but will not be limited to plasma and serum proteins, immunophenotyping, gene expression, CCI [redacted], and genotyping.

Because biomarker science is a rapidly evolving area of investigation, and adverse events in particular are difficult to predict, it is not possible to specify prospectively all tests that will be done on the specimens provided. Biomarkers may be modified during or after the end of the study to remove tests no longer indicated and/or to add new tests based upon the growing state of art knowledge. CCI [redacted]

CCI [redacted]

[redacted]

CCI [redacted]

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately thirty (30) subjects who meet the inclusion/exclusion criteria will be enrolled. Subjects who discontinue study participation before completion of all doses for reasons other than study treatment related adverse events may be replaced. Eligible subjects may roll over from study GS-US-382-1450 and continue onto the ATI phase of GS-US-382-3961. Sponsor and Investigator will determine GS-US-382-1450 subject's eligibility to enter the ATI phase in the GS-US-382-3961 study based criteria including on their pre-ART CD4 and HIV-1 RNA values, documentation of <50 copies/mL at the End of Study Visit and safety profile in GS-US-382-1450.

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) HIV-1 infected subjects of ≥ 18 years at Pre-Baseline/Day -13

3) Chronic HIV-1 infection (for ≥6 months) prior to ART initiation

4) Pre-ART Plasma HIV-1 RNA set point between 50 and ≤5,000 copies/mL measured within two years prior to ART initiation calculated as below:

   - At least one plasma HIV-1 RNA level, while off ART, above the level of detection using standard assays (<40 copies/mL Abbott, <50 copies/mL Roche, < 75 copies/mL bDNA) and ≤5000 copies/mL prior to ART initiation.

   - Using all available viral load determinations during the two years prior to ART, the mean HIV-1 RNA viral load (defined as viral load set point) must be above the limit of detection and ≤5000 copies/mL (those determinations below the level of quantification will be considered as detectable at this threshold level). Two years of prior data are not required but up to two years of data will be evaluated.

5) On ART regimen for ≥ 6 consecutive months prior to screening

   - The following agents are allowed as part of the current ART regimen: NRTIs, raltegravir, dolutegravir, rilpivirine, and maraviroc

   - A change in ART regimen ≥45 days prior to Pre-Baseline/ Day -13 for reasons other than virologic failure (eg, tolerability, simplification, drug-drug interaction profile) is allowed.

6) Plasma HIV-1 RNA levels <50 copies/mL at screening

7) Documented plasma HIV-1 RNA < 50 copies/mL for ≥ 6 months preceding the Screening visit (or undetectable HIV-1 RNA level according to the local assay being used if the limit of detection is ≥ 50 copies/mL).

   - Unconfirmed virologic elevations of ≥ 50 copies/mL (transient detectable viremia, or "blip") prior to screening are acceptable. (If the lower limit of detection of the local HIV-1 RNA assay is < 50 copies/mL, the plasma HIV-1 RNA level cannot exceed 50 copies/mL on two consecutive HIV-1 RNA tests)

   - If ART regimen is changed ≥ 45 days prior to Pre-Baseline/Day -13, plasma HIV-1 RNA <50 copies/mL at Pre-baseline/Day -13 visit is required.

8) Availability of a fully active alternative ART regimen, in the opinion of the Investigator, in the event of discontinuation of the current ART regimen with development of resistance.

9) All subjects must agree to utilize male or female condoms during sexual activity, or practice sexual abstinence for the duration of the study.

10) Females of childbearing potential must agree to utilize highly effective contraception methods (as described in Appendix 5) or be non-heterosexually active or practice sexual abstinence from screening through the duration of study treatment and for 36 days following the last dose of study drug.

   - Female subjects who utilize hormonal contraceptive as one of their birth control methods must have used the same method for at least three months prior to study dosing

   - Female subjects who have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure must have a serum follicle stimulating hormone (FSH) level at screening within the post-menopausal range based on the Central Laboratory reference

11) Male subjects must agree to utilize a highly effective method of contraception during heterosexual intercourse (as described in Appendix 5) or practice sexual abstinence from screening throughout the study period and for 90 days following discontinuation of investigational medicinal product.

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 90 days prior to screening (refer to Appendix 6)

2) Chronic hepatitis B infection as determined by either:

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

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

3) Hepatitis C antibody (HCVAb) positive

   - Positive anti-HCV antibody and negative HCV PCR results are acceptable

4) Hemoglobin < 11.5 g/dL (males) or < 11 g/dL (females)

5) White blood cells <2,500 cells/μL

6) Platelets < 125,000/mL

7) Absolute Neutrophil Count < 1000 cells/μL

8) CD4 count < 500 cells/μL

9) Alanine aminotransferase (ALT), aspartate aminotransferase (AST) or bilirubin > 2 × upper limit of normal (ULN)

10) Estimated glomerular filtration rate < 60 mL/min to the Cockcroft-Gault formula for creatinine clearance {Cockcroft 1976}:

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

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

11) Documented history of pre-ART CD4 nadir < 200 cells/μL

   - Unknown pre-ART CD4 nadir is acceptable

12) Females who are pregnant (as confirmed by positive serum pregnancy test)

13) Females who are breastfeeding

14) Autoimmune disease requiring on-going immunosuppression

15) Acute febrile illness within 35 days prior to Pre-Baseline/Day -13

16) Participation in any other clinical trial (including observational trials) without prior approval from the sponsor is prohibited while participating in this trial

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

18) History or presence of allergy or intolerance to the study drug, the metabolites or formulation excipient

19) Documented history of resistance to any components of the current ART regimen

20) Any vaccination or immunomodulatory concomitant medication within 30 days prior to Pre-Baseline/Day -13. Elective vaccination (eg flu shot, hepatitis A or B vaccine) during the course of the study will require prior approval from Sponsor.

21) Subjects receiving ongoing therapy with any of the medications listed in Section 5.4. Administration of any disallowed medications must be discontinued at least 14 days prior to Pre-Baseline/Day -13 visit. Refer to the current Prescribing Information for the medications that are contraindicated with the current ART regimen

22) 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 dosing requirements.

23) History of autoimmune disease (e.g. lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, sarcoidosis, moderate or severe psoriasis)

4.4. Other Protocol Restrictions

Subjects will be encouraged to avoid strenuous or prolonged exercise, as well as saunas, steam baths, and sunbathing or other prolonged UV exposure, (eg in a tanning salon) from the screening evaluation until completion of end of study procedures, as these activities are known to affect certain clinical laboratory test parameters, (eg CPK) and may provide false indicators of a potentially treatment-related toxicity.

Subjects will also be prohibited from blood donation (in excess of that required for clinical care) within 30 days prior to Screening and 30 days after end of study.

Smokers and other current tobacco users should keep their tobacco use relatively consistent while enrolled in the study. Non-smokers or ex-smokers should not start or resume smoking.

Other restrictions include all illegal or illicit drug use and use of prescription drugs outside the care of the prescribing physician.

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.

The subject number assignment may be performed ± 3 days of the in-clinic Pre-Baseline/Day -13 visit, provided that all other screening procedures have been completed and subject eligibility has been confirmed. Once a subject number has been assigned, it will not be reassigned to any other subject.

Eligible subjects (n= 30) will be randomized in a 2:1 ratio to receive GS-9620 8 mg or placebo-to-match.

Randomization will be stratified by pre-ART viral load (≥50 to < 2000 copies/mL or ≥2000 to ≤5000 copies/mL) at screening.

Subjects will be responsible to continue to source their anti-retroviral medications. Investigator must provide the prescription to the subject for their anti-retroviral medications.

Clinical Packaging & Labeling for purposes of managing blinded labeling and Clinical Supply Management for purposes of inventory management will remain unblinded throughout the study to prepare and manage the study drug. The Pharmacokinetics File Administrator, or designee, who facilitates data transfer of PK files between Gilead and vendors, will remain unblinded.

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 for that subject. Detailed instructions for study treatment assignment unblinding will be provided to the investigator by the Sponsor. 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 subject's emergency medical care. 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 case 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 Drug Safety and Public Health (PVE) may independently unblind cases for expedited reporting of suspected unexpected serious adverse reactions (SUSARs).

5.2. Description and Handling of GS-9620 and Placebo-to-match GS-9620

5.2.1. Formulation

An 8 mg dose of GS-9620 will be administered as four 2 mg strength tablets. The tablets are round, biconvex, plain-faced, and film-coated white.

GS-9620 tablets contain the following inactive ingredients: lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Placebo-to-match GS-9620 tablets are round, biconvex, plain-faced, and film-coated white.

Placebo tablets contain lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

5.2.2. Packaging and Labeling

GS-9620 tablets and placebo-to-match tablets are packaged in white, high density polyethylene bottles. Each bottle contains up to 5 tablets, silica gel desiccant, and polyester packing material. Each bottle is capped with a child-resistant polypropylene screw cap fitted with an induction sealed, aluminum-faced liner.

Study drug(s) to be distributed to centers in the US shall be labeled to meet applicable requirements of the United States Food and Drug Administration (FDA) and/or other local regulations.

5.2.3. Storage and Handling

GS-9620 and placebo-to-match tablets should be stored at controlled room temperature of 25 °C (77 °F); excursions are permitted between 15 °C and 30 °C (59 °F and 86 °F). Storage conditions are specified on the label.

Until dispensed to the subjects, bottles of GS-9620 and placebo-to-match should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of the tablets and proper product identification, the drug products should be stored in the containers in which they are supplied. Keep the bottles tightly closed.

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 GS-9620.

5.3. Dosage and Administration of GS-9620

On dosing days, GS-9620 or placebo-to-match should be taken by subject with approximately 240 mL of water on an empty stomach (i.e. no food or liquids, except water for at least 2 hours prior to dosing; overnight fasting is preferable). If subjects eat prior to the 2 hour fasting period before GS-9620 dosing, no more than a light meal should be eaten. Subjects will not be allowed to consume water 1 hour before and 2 hours after dosing, except for the 240 mL with the study treatment. Subjects should remain fasting without food until 2 hours after dosing. Subjects will be asked to provide information on food consumption and total fasting time prior to dosing.

5.4. Prior and Concomitant Medications

No clinical drug-drug interaction studies have been conducted with GS-9620.
GS-9620 is predominantly metabolized by CYP3A with minor contribution of CYP2C8 and CYP2D6 in vitro, and was shown to be a substrate of P-gp and BCRP in vitro. GS-9620 plasma exposures may increase or decrease on co-administration with CYP3A/P-gp/BCRP inhibitors or inducers.

ART agents known to inhibit or induce CYP3A/P-gp/BCRP are excluded from use in this protocol. The following agents are NOT allowed as part of the current ART regimen: HIV protease inhibitors (including low dose ritonavir), cobicistat-containing regimens, elvitegravir, efavirenz, etravirine and nevirapine.

Concomitant use of herbal/natural supplements with GS-9620 may result in pharmacokinetic interactions resulting in alterations in exposure of GS-9620. Administration of GS-9620 with grapefruit juice or Seville orange juice may result in higher exposures to GS-9620. Subjects will refrain from consumption of grapefruit juice, grapefruits, and Seville orange juice throughout participation in the study.

Subjects are restricted from receiving therapy with any medication listed in Table 5-1. Administration of any of the disallowed medications listed in Table 5-1 must be discontinued at least **14** days prior to the Pre-Baseline/Day -13 and through completion of treatment or the Early Study Drug Discontinuation Visit. **Any medications not on the list must be reviewed with the Sponsor prior to randomization and during the study treatment period.** Vitamins and/or acetaminophen and/or ibuprofen and/or hormonal contraceptive medications are exceptions and are allowed during the study period. No immunomodulatory concomitant medications are allowed for at least 30 days prior to Pre-Baseline/Day -13.

Subjects' ART regimens must be used in accordance with their Prescribing Information.

At clinically achieved plasma concentrations, GS-9620 is not expected to be a perpetrator of systemic drug-drug interactions. GS-9620 concentrations estimated to be achieved in the gut at the ≥10 mg GS-9620 doses may transiently inhibit intestinal P-gp and increase systemic exposures of the drugs that are known P-gp substrates. It is recommended that oral P-gp substrates are administered with caution in combination with GS-9620 ≥10 mg doses.

Table 5-1. Prohibited Concomitant Medications

Drug Class	Agents Disallowed	Use Discouraged and To be Used with Caution
Acid Reducing Agents	Proton Pump Inhibitors	H2-receptor antagonists[a]
ACAT inhibitor	Avasimibe	
ACE Inhibitors	Captopril	
Analeptic	Modafinil	
Angiotensin II inhibitors	Telmisartan	
Anti-anginals	Ranolazine	
Anti-arrhythmics	Amiodarone, Dronedarone, Quinidine	
Antibiotics	Azithromycin, Clarithromycin, Erythromycin, Nafcillin, Telithromycin	Ciprofloxacin, Trimethoprim
Anticonvulsants	Carbamazepine, Phenytoin, Phenobarbital, Oxcarbazepine	
Antidepressants	Nefazodone, Venlafaxine, Ziprasidone, Paroxetine	
Antidiabetics	Pioglitazone	
Anti-epileptics	Divalproex	
Antiemetics		Aprepitant, Casopitant
Antifungals	Caspofungin, Ketoconazole, Itraconazole, Voriconazole, Posaconazole, Fluconazole	
Antimycobacterials	Rifampin, Rifampentine, Rifabutin, Isoniazid	
Antiretroviral Agents	HIV Protease Inhibitors (including low dose Ritonavir), Cobicistat-containing regimens, Elvitegravir, Efavirenz, Etravirine and Nevirapine	
Beta-Blockers	Carvedilol, Talinolol	
Calcium Channel Blockers	Diltiazem, Felodipine Mibefradil, Nicardipine, Nifedipine, Nitrendipine, Verapamil	
Diuretics	Conivaptan	
Endothelin Receptor Antagonists	Bosentan	
Herbal/Natural Supplements*	St. John's Wort, Echinacea, Gingko, Milk thistle, Chinese herb shosaiko-to (or Xiao-Shai-Hu-Tang)	
HMG-Coa Reductase Inhibitors	Atorvastatin,	Pitavastatin, Pravastatin, Rosuvastatin, Lovastatin, Fluvastatin, Simvastatin
Immunosuppressants	Cyclosporine, Rapamycin, Sirolimus, Tacrolimus	
Systemic Corticosteroids	All agents, including dexamethasone	Use of Prednisone as a steroid burst (≤ 1 week of use) should be monitored appropriately
Systemic Chemotherapeutic (antineoplastic) Agents	All agents	

a Dose not to exceed 20 mg famotidine or equivalent and dose should be administered not less than 24 hours prior to dosing with GS-9620 and not less than 12 hours after dosing with GS-9620.
* Use of complementary or alternative medicines is prohibited at least 14 days prior to Dose 1-Day 1 through the end of the follow-up

Should subjects have a need to initiate treatment with any concomitant medication, the Gilead Medical Monitor must be consulted prior to initiation of the new medication. In instances where a 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 medication.

5.5. Accountability for GS-9620

The investigator is responsible for ensuring adequate accountability of all used and unused IMP (Investigational Medicinal Product). 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.

GS-9620 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, the IMP kit number dispensed
- Record the date, quantity of used and unused IMP returned, along with the initials of the person recording the information.

5.5.1. Investigational Medicinal Product Return or Disposal

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. If drug is destroyed on site, the investigator must maintain accurate records for all study drug bottles destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and person who disposed of the drug. All study drug records must be maintained at the site and copies must be submitted to Gilead Sciences at the end of the study.

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

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 described in the text that follows.

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

6.1. Subject Enrollment and Treatment Assignment

It is the responsibility of the Investigator to ensure that subjects are eligible for study prior to enrollment. Please refer to Section 6.2 for details about randomization and treatment assignment.

6.2. Pretreatment Assessments (Period 1)

6.2.1. Screening Visit

Subjects will be screened within 35 days before Pre-Baseline/Day -13 to determine eligibility for participation in the study. The following will be performed and documented at screening after obtaining written informed consent:

- Obtain medical history including route and estimated duration of HIV-1 infection, history of HIV-1 disease-related events, anti-retroviral treatment (ART) history for at least 6 months and prior medications within 35 days of the screening visit
- Obtain pre-ART viral load set point
- Collect pre-ART CD4 nadir, and historical genotype(s), if available
- Obtain HLA class I and II type through available records, if available or obtain blood sample for testing
- Complete physical examination. Urogenital/anorectal exams will be performed at the discretion of the Investigator
- Vital signs (blood pressure, pulse, respiration rate and temperature)
- Body weight, and height
- 12-lead ECG performed supine
- Obtain urine for urinalysis

- Obtain blood samples for:

  — Serum pregnancy test (females of childbearing potential only). If the test is positive, the subject will not be enrolled

  — Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid

  — Metabolic assessments: 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). 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.

  — Estimated GFR according to the Cockcroft-Gault formula for creatinine clearance:

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

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

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

  — CD4+ cell count, CD8 cell count, CD4/CD8 ratio and CD4 %

  — Plasma HIV-1 RNA by TaqMan® v2.0

  — Hepatitis B virus serology

  — Hepatitis C virus serology

  — Plasma ART trough PK

Record any serious adverse events and all adverse events related to protocol mandated procedures occurring after signing of the consent form.

In order to establish eligibility, Investigators may repeat screening procedures or laboratory assessments for subjects who have an acute illness or abnormal laboratory value that is expected to resolve without sequelae within the screening window.

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 35 days after screening for Pre-Baseline/Day -13 and randomization into the study.

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

6.2.2. Pre-Baseline/Day -13 Assessments

The following evaluations are to be completed at the Pre-Baseline/Day -13 visit. The Pre-Baseline/Day -13 visit is to be completed within 35 days of Screening.

- Review of Inclusion/Exclusion criteria to confirm subject eligibility
- Review of AEs and changes in concomitant medications
- Review medical history
- Symptom-directed physical examination as needed
- Blood sample collection for the following laboratory analyses:
  - Plasma HIV-1 RNA by TaqMan® v2.0
  - Plasma HIV-1 RNA by SCA
  - TLR7 genotyping
  - PBMC associated viral RNA and DNA by CAVR and CAVD
  - CCI [redacted]
  - T cell ICS
  - Immune cell activation and phenotyping
  - Serum antibody profiling assays
  - CCI [redacted]
  - CCI [redacted]
  - CCI [redacted]

6.2.3. Randomization

Obtain subject number and randomize the subject. The subject number assignment and randomization may be performed ±3 days of the in-clinic Pre-Baseline/Day -13 visit provided that all screening procedures have been completed and subject eligibility has been confirmed.

If subject's ART regimen is changed ≥ 45 days prior to Pre-Baseline/Day -13, plasma HIV-1 RNA <50 copies/mL at Pre-Baseline/Day -13 visit is required to confirm eligibility.

6.2.4. Dose 1-Day 1 Assessments

Subjects are to arrive in a fasting state for the Dose 1-Day 1 visit. Food will not be permitted between at least 2 hours prior to and until 2 hours after dosing. Overnight fasting is preferred. Aside from the 240 mL of water provided at dosing, water/liquids will not be permitted from 1 hour prior to until 2 hours after dosing. If subjects eat prior to the 2 hour fasting period before study drug dosing, no more than a light meal should be eaten.

The subject must complete all Dose 1-Day 1 procedures (except for post-dose PK collection) before being dispensed the study drug. Initiation of the treatment with the study drug must take place in the clinic and will be administered by blinded study staff. **Subjects will remain on-site for 10 hours after the first dose for safety assessments and phlebotomy.** The visit should occur within 13 day±1 day from Pre-Baseline/Day -13. The following evaluations are to be completed at the Dose 1-Day 1 Visit:

- Review medical history
- Review of AEs and changes in concomitant medication
- Symptom-directed physical examination as needed
- Vital signs (blood pressure, pulse, respiration rate and temperature)
- Weight
- VAS Adherence Questionnaire to be completed by the subject. Subject is to read questionnaire by himself/herself and write/mark answers directly onto questionnaires.

- Urine collection for the following laboratory procedures:
  - Urine pregnancy test (females of childbearing potential only). If the urine pregnancy test is positive at Dose 1-Day 1, study drug will not be dispensed. The positive result will be confirmed with a serum pregnancy test. If the serum pregnancy test is positive, the subject will not be able to participate.
  - Urinalysis
- Blood sample collection for the following laboratory analyses:
  - Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid
  - Hematology profile: complete blood count (CBC) with differential and platelet count
  - Estimated glomerular filtration rate according to the Cockcroft-Gault formula for creatinine clearance
  - CD4+ cell count, CD8 cell count, CD4/CD8 ratio and CD4 %
  - Plasma HIV-1 RNA by TaqMan® v2.0
  - Whole blood ISG mRNA panel
  - Cytokine, chemokines
  - GS-9620 Pharmacokinetic assessments - Intensive PK samples will be collected at Pre-dose (≤ 5 minutes prior to dosing), 0.5, 1, 2, 4, 6, 8, 10 and 24 hours post dose at Dose 1-Day 1 visit.

[redacted]

- In-Clinic Dosing
- Collect information on food consumption and total fasting time prior to fasting
- Provide instructions to contact the clinic immediately if any flu-like symptoms are noted (eg: fatigue, pyrexia, chills, myalgia, joint pain or headache)

6.3. Treatment Assessments (Period 1)

6.3.1. Treatment Assessments on Dosing Visits Dose 2- Dose 10

These study visits are to be scheduled at an interval of 14 days with visit window of ± 1 day relative to the previous dosing visit if next dose is uninterrupted. The following procedures will be performed. The procedures are to be completed prior to dosing at each visit.

Study Procedure/Visit	Dose 2-Day 1	Dose 3-Day 1	Dose 4-Day 1	Dose 5-Day 1	Dose 6-Day 1	Dose 7-Day 1	Dose 8-Day 1	Dose 9-Day 1	Dose 10-Day 1
Review of AEs and changes in concomitant medications	X	X	X	X	X	X	X	X	X
Symptom Directed Physical Examination as needed	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X
Blood collection for									
CD4+ cell count, CD8 cell count, CD4/CD8 ratio and CD4 %	X	X	X	X	X	X	X	X	X
Chemistry Profile	X	X	X	X	X	X	X	X	X
Hematology Profile	X	X	X	X	X	X	X	X	X
Plasma HIV-1 RNA by Taqman® 2.0	X	X	X	X	X	X	X	X	X
Plasma HIV-1 RNA by SCA			X		X				X
PBMC associated viral RNA and DNA by CAVR and CAVD			X		X				X
CCI									
Whole blood ISG mRNA panel			X						X
Cytokine, chemokines			X						X
Immune cell activation and phenotyping			X						
CCI									
VAS Questionnaire			X				X		
Urine collection for:									
Urine Pregnancy Test (females of childbearing potential only)	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X
Review DLTs to confirm dosing can proceed[a]	X	X	X	X	X	X	X	X	X
In-Clinic Dosing[b]	X	X	X	X	X	X	X	X	X

a Prior to the subject being administered the in-clinic dose, the Investigator must verify the subject's continued eligibility for in-clinic dosing, including the absence of Dose Limiting Toxicities (DLTs) described in Section 7.6.1.
b All doses will be directly administered to the study subject by blinded site staff.

If the urine pregnancy test is positive at a dosing visit, study drug will not be dispensed. The positive result will be confirmed with a serum pregnancy test. If the serum pregnancy test is positive, the subject will be discontinued from the study.

Chemistry profile includes alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid.

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

If HIV-1 RNA viral load will be >5,000 copies/mL at any visit post Dose, viral load will be observed at next scheduled visit or retested within 4 days. The next dose will be withheld and only be given if viral load of ≤5,000 copies/mL is achieved. The study procedure schedule will be reset relative to the next dose of GS-9620.

On dosing days, GS-9620 or placebo-to-match should be taken by subject with approximately 240 mL of water on an empty stomach. Food will not be permitted between at least 2 hours prior to and until 2 hours after dosing. Aside from the 240 mL of water provided at dosing, water/liquids will not be permitted from 1 hour prior to until 2 hours after dosing. If subjects eat prior to the 2 hour fasting period before study drug dosing, no more than a light meal should be eaten. Subjects will be asked to provide information on food consumption and total fasting time prior to dosing.

These fasting guidelines should be followed by subjects on ***all*** dosing days.

At each visit, instructions will be provided to subjects to contact the clinic immediately if any flu-like symptoms are noted (e.g.: fatigue, pyrexia, chills, myalgia, joint pain or headache)

6.3.2. Treatment Assessments on Non Dosing Days

All study visits are to be scheduled relative to each dosing day visit. All study visits listed above **except for Dose 1-Day 2** allow a visit window of ± 1 day of the protocol specified visit. These visits may occur at the investigator site or at other location agreed by subject by mobile nurse vendor. The following procedures will be performed:

Study Procedure/ Visit	**Dose 1-Day 2**	**Dose 1-Day 8**	**Dose 2-Day 8**	**Dose 3-Day 8**	**Dose 4-Day 2**	**Dose 4-Day 4**	**Dose 4-Day 8**	**Dose 5-Day 8**	**Dose 6-Day 4**	**Dose 6-Day 8**	**Dose 7-Day 8**	**Dose 8-Day 8**	**Dose 9-Day 8**	**Dose 10-Day 2**	**Dose 10-Day 4**	**Dose 10-Day 8**	**Dose 10-Day 14**
Review of AEs and changes in concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Symptom Directed Physical Examination as needed	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs																	X
Weight																	X
CCI																	
Blood collection for																	
CD4+ cell count, CD8 cell count, CD4/CD8 ratio and CD4 %																	X
Plasma GS-9620 Intensive PK	X																
Plasma ART Trough PK									X								
Plasma HIV-1 RNA by Taqman® 2.0	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Plasma HIV-1 RNA by SCA					X	X			X					X	X		X

Study Procedure/ Visit	Dose 1-Day 2	Dose 1-Day 8	Dose 2-Day 8	Dose 3-Day 8	Dose 4-Day 2	Dose 4-Day 4	Dose 4-Day 8	Dose 5-Day 8	Dose 6-Day 4	Dose 6-Day 8	Dose 7-Day 8	Dose 8-Day 8	Dose 9-Day 8	Dose 10-Day 2	Dose 10-Day 4	Dose 10-Day 8	Dose 10-Day 14
PBMC associated viral RNA by CAVR and CAVD					X	X			X					X	X		X
CCI																	
CCI																	
Whole blood ISG mRNA	X				X									X			
Cytokine, chemokines	X	X			X		X							X		X	
T cell ICS																	X
Immune cell activation, phenotyping					X												X
Serum for antibody profiling assays																	X
Inflammatory biomarkers																	X
CCI																	
Urine collection for urine pregnancy test																	X
CCI																	

Study Procedure/ Visit	Dose 1-Day 2	Dose 1-Day 8	Dose 2-Day 8	Dose 3-Day 8	Dose 4-Day 2	Dose 4-Day 4	Dose 4-Day 8	Dose 5-Day 8	Dose 6-Day 4	Dose 6-Day 8	Dose 7-Day 8	Dose 8-Day 8	Dose 9-Day 8	Dose 10-Day 2	Dose 10-Day 4	Dose 10-Day 8	Dose 10-Day 14
CCI																	

If the urine pregnancy test is positive at a dosing visit, study drug will not be dispensed. The positive result will be confirmed with a serum pregnancy test. If the serum pregnancy test is positive, the subject will be discontinued from the study.

Subject will be reminded to contact the clinic immediately if any flu-like symptoms are noted (eg: fatigue, pyrexia, chills, myalgia, joint pain or headache).

6.4. Post-treatment Assessments (Period 2)

6.4.1. Analytical treatment interruption Visit 1

This visit will occur 28 days (± 3 days) after Dose 10-Day 1 Visit provided plasma HIV-1 RNA viral load is <50 copies/mL at Dose 10-Day 14. For subjects with HIV-1 RNA viral load >50 copies/mL at Dose 10-Day 14, the ATI Visit 1 will only occur if undetectable viral load is achieved within two re-test measurements. Subjects will take their last dose of ART on the day prior to ATI Visit 1.

Eligible subjects may roll over from study GS-US-382-1450 and continue onto the ATI phase of GS-US-382-3961. Sponsor and Investigator will determine GS-US-382-1450 subject's eligibility to enter the ATI phase in the GS-US-382-3961 study based on criteria including their pre-ART CD4 and HIV-1 RNA values, documentation of <50 copies/mL at the End of Study Visit and safety profile in GS-US-382-1450. For these subjects, ATI Visit 1 will occur approximately within 2 weeks of completing End of Study visit on GS-US-382-1450.

The following evaluations and/or procedures will be performed:

- Review of AEs and changes in concomitant medications
- Complete physical examination
- Vital signs (blood pressure, pulse, respiration rate and temperature)
- Weight

- Blood sample collection for the following laboratory analyses:
  - CD4+ cell count, CD8 cell count, CD4/CD8 ratio and CD4 %
  - Plasma HIV-1 RNA by TaqMan® v2.0
  - Chemistry profile : alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid
  - Hematology profile: complete blood count (CBC) with differential and platelet count
  - Estimated glomerular filtration ate according to the Cockcroft-Gault formula for creatinine clearance
- Urine collection for the following laboratory procedures:
  - Urine pregnancy test (females of childbearing potential only). If the urine pregnancy test is positive, the positive result will be confirmed with a serum pregnancy test. If the serum pregnancy test is positive, the subject will be discontinued from the study
  - Urinalysis

6.4.2. ATI visits 2-24 (once/week) beginning at ATI Visit 1

The visits will occur weekly and should be scheduled at least 5 days apart. The first visit should occur at least 5 days after ATI Visit 1. The following procedures will be conducted at all visits unless otherwise stated. The visits may occur at investigator site or at agreed upon location by subject by mobile nurse vendor.

- Review of AEs and changes in concomitant medications
- Symptom directed physical examination as needed (Visits 3, 7, 11, 15, 19, 23)
- Complete physical examination. Urogenital/anorectal exams will be performed at the discretion of the Investigator (Visits 5, 9, 13, 17, 21)
- Vital signs (blood pressure, pulse, respiration rate and temperature) (Visits 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23)
- Weight (Visits 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23)
- Blood sample collection for the following laboratory analyses:
  - Chemistry profile : alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid (Visits 5, 9, 13, 17, 21)

- Hematology profile: complete blood count (CBC) with differential and platelet count (Visits 5, 9, 13, 17, 21)
- Estimated glomerular filtration ate according to the Cockcroft-Gault formula for creatinine clearance (Visits 5, 9, 13, 17, 21)
- CD4+ cell count, CD8+ cell count, CD4/CD8 ratio and CD4 %
- Plasma HIV-1 RNA by TaqMan® v2.0

- Urine collection for the following laboratory procedures:
  - Urine pregnancy test (females of childbearing potential only). If the urine pregnancy test is positive, the positive result will be confirmed with a serum pregnancy test. If the serum pregnancy test is positive, the subject will be discontinued from the study (Visits 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23)
  - Urinalysis (Visits 5, 9, 13, 17, 21)

During the ATI period, if HIV-1 RNA becomes > 50 copies/mL, the visit schedule for HIV-1 RNA values may be adjusted per Investigator discretion.

ART should also be re-initiated if subject meets the criteria defined in Section 6.6.1

6.4.3. ATI Remission Visit

This visit will be planned after completion of 12 weeks of ATI for subjects with plasma HIV-1 RNA <50 copies/mL in the absence of ART re-initiation. The visit will occur approximately within 2 weeks of subjects achieving HIV-1 viral load <50 copies/mL at or after ATI Visit 12 CCI [redacted]. The following procedure will be followed:

- Review of AEs and changes in concomitant medications
- Complete physical examination. Urogenital/anorectal exams will be performed at the discretion of the Investigator
- Vital signs (blood pressure, pulse, respiration rate and temperature)
- Weight
- Blood sample collection for the following laboratory analyses:
  - CD4+ cell count, CD8 cell count, CD4/CD8 ratio and CD4 %
  - Plasma HIV-1 RNA by TaqMan® v2.0
  - Plasma HIV-1 RNA by SCA
  - PBMC associated viral RNA and DNA by CAVR and CAVD

CCI [redacted]

— Cytokines, chemokines

— T cell ICS

— Immune cell activation and phenotyping

— Serum for antibody profiling assays

CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

- Urine collection for the following laboratory procedures:

  — Urine pregnancy test (females of childbearing potential only). If the urine pregnancy test is positive, the positive result will be confirmed with a serum pregnancy test. If the serum pregnancy test is positive, the subject will be discontinued from the study.

6.5. Post-treatment Extension Assessments (Period 3)

CCI [redacted]

[redacted]

6.5.2. End of Study Visit for subjects who have not re-initiated ART anytime through Period 2 and 3

End of Study Visit will occur for subjects who have continued the study through Period 2 and 3 and have not re-initiated ART. The Visit will occur 1 week after completion of the last ATI visit. For the purpose of scheduling the end of study visit, a ± 1 days window may be used.

ART Re-initiation post the End of Study Visit will be up to the subject's health care provider discretion.

The following evaluations and/or procedures will be performed at the end of study visit:

- Review of AEs and changes in concomitant medications
- Symptom directed physical examination as needed
- Vital signs (blood pressure, pulse, respiration rate and temperature)
- Weight

- Blood sample collection for the following laboratory analyses:
  - Chemistry profile : alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid
  - Hematology profile: complete blood count (CBC) with differential and platelet count
  - Metabolic assessments: 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). 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.
  - CD4+ cell count, CD8 cell count, CD4/CD8 ratio and CD4 %
  - Plasma HIV-1 RNA by TaqMan® v2.0
  - Estimated glomerular filtration rate according to the Cockcroft-Gault formula for creatinine clearance
- Urine collection for
  - Urinalysis
  - Urine pregnancy test (females of childbearing potential only). Positive urine pregnancy test will be confirmed with serum test

6.6. ART Re-initiation and Post Re-Suppression Visits (may occur in Period 2 or Period 3)

6.6.1. ART Re-initiation Visits

During the 24 week ATI period (Visits 2-24) CCI [redacted], ART will be re-initiated if any of the criteria below are met:

- if HIV-1 RNA is >10,000 copies/mL on four consecutive weekly measurements OR
- if HIV-1 RNA does not decrease to <1,000 copies/mL within 6 weeks of virologic rebound OR
- if CD4+ cell count is confirmed to decrease by >30% from pre-ATI levels OR
- if CD4+ cell count is confirmed <350 cells/µL OR
- Per Investigator or Sponsor's discretion due to other clinical criteria

Principal investigator will construct the regimen per his/her discretion. The visits will occur weekly until plasma viral load is <50 copies/mL and then every other week until two consecutive measures are undetectable.

If/when HIV-1 RNA is > 1,000 copies/mL during the ATI[redacted] or undetectable viral load is not achieved within 4 weeks of ART re-initiation (and if viral load is ≥200 copies/mL), resistance testing will be performed at the next visit.

Once the initial 24 weeks of ATI are completed, subjects who restart ART will complete ART Re-Initiation Visits per frequency stated above. A window of ±3 days may be used to schedule these visits.

The following procedures will be performed at these visits:

- Review of AEs and changes in concomitant medications
- Vital signs (blood pressure, pulse, respiration rate and temperature)
- Blood sample collection for the following laboratory analyses:
  - CD4+ cell count, CD8+ cell count, CD4/CD8 ratio and CD4 %
  - Plasma HIV-1 RNA by TaqMan® v2.0
- Urine collection for following analyses at the first ART re-initiation visit and then once a month until Post ART Re-suppression Visits
  - Urine pregnancy test (females of childbearing potential only). Positive urine pregnancy test will be confirmed with serum test

6.6.2. Post-ART Re-suppression Visits 1-6

These visits will occur monthly for 6 months after the subject has completed necessary ART Re-Initiation Visits.A window of ± 6 days may be used to schedule this visit.

The following procedures will be followed at Visits 1-5:

- Review of AEs and changes in concomitant medications
- Vital signs (blood pressure, pulse, respiration rate and temperature)
- Blood sample collection for the following laboratory analyses:
  - Chemistry profile : alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid
  - Hematology profile: complete blood count (CBC) with differential and platelet count
  - CD4+ cell count, CD8+ cell count, CD4/CD8 ratio and CD4 %
  - Plasma HIV-1 RNA by TaqMan® v2.0

- Urine collection for
  - Urinalysis
  - Urine pregnancy test (females of childbearing potential only). Positive urine pregnancy test will be confirmed with serum test.

The following procedure will be followed at Post-ART Re-suppression Visit 6:

- Review of AEs and changes in concomitant medications
- Symptom-directed physical examination as needed
- Vital signs (blood pressure, pulse, respiration rate and temperature)
- Weight
- Blood sample collection for the following laboratory analyses:
  - Chemistry profile : alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid
  - Hematology profile: complete blood count (CBC) with differential and platelet count
  - CD4+ cell count, CD8 cell count, CD4/CD8 ratio and CD4 %
  - Plasma HIV-1 RNA by TaqMan® v2.0
  - HIV-1 reservoir measurements using plasma SCA, CAVR, CAVD
  - CCI [redacted]
- Urine collection for
  - Urinalysis
  - Urine pregnancy test (females of childbearing potential only). Positive urine pregnancy test will be confirmed with serum test.

6.6.3. Assessments for Premature Discontinuation from Study

Subjects who prematurely discontinue study drug prior to completing Dose 10 will be required to complete an Early Study Drug Discontinuation Visit (ESDD) within 30 days after their last dose of study treatment.

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 6.7, 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.

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

The following evaluations are to be completed at the Early Study Drug Discontinuation Visit:

- Review of AEs and changes in concomitant medication
- Symptom-directed physical examination as needed
- Vital signs (blood pressure, pulse, respiration rate and temperature)
- Weight
- Blood sample collection for the following laboratory analyses:
  - Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid
  - Estimated glomerular filtration rate according to the Cockcroft-Gault formula for creatinine clearance
  - Hematology profile: complete blood count (CBC) with differential and platelet count
  - Plasma HIV-1 RNA by TaqMan® v2.0
  - CD4+ cell count, CD8+ cell count, CD4/CD8 ratio and CD4 %
  - Cytokine, chemokines
  - Whole blood ISG mRNA panel
- Urine collection for the following laboratory procedures:
  - Urinalysis
  - Urine pregnancy test (females of childbearing potential only). Positive urine pregnancy test will be confirmed with serum test

6.7. Criteria for Discontinuation of Study Treatment

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.
- Unacceptable toxicity, 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 receives GS-9620 and experiences one or more DLTs (at discretion of SEC)
- Subject request to discontinue for any reason
- Subject noncompliance
- Pregnancy during the study; refer to Appendix 5
- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC)

CCI [redacted]

[redacted]

6.9. Prolonged Viremia During GS-9620 Dosing Phase

Subjects will be considered to have prolonged viremia if they have at least two consecutive plasma HIV-1 RNA levels ≥ 5000 copies/mL during a single dosing period.

6.9.1. Management of Prolonged Viremia During GS-9620 Dosing Phase

If HIV-1 RNA viral load is >5000 copies/mL at any visit post Dose, viral load will be tested at next scheduled visit or retested within 4 days. The next dose will be withheld and only given after viral load of ≤5000 copies/mL is achieved. The study procedure schedule will be reset relative to the next dose of GS-9620.

If HIV-1 RNA viral load >5000 copies/mL is confirmed during a single dosing period, then this subject will be considered to have prolonged viremia and blood samples from this visit will be used for HIV-1 genotype/phenotype testing with assays corresponding to the antiretroviral medications the subject is taking.

If primary resistance mutations to the subject's existing ART regimen are identified, a new ART regimen will be configured at the discretion of the Investigator and the subject will be discontinued from the study. If the genotyping/phenotyping assay fails to provide results or no drug resistance mutations are identified, a new ART regimen may be configured at the discretion of the Investigator. Subjects who start a new ART regimen will not be allowed to receive further doses of study drug, but can be monitored for the study duration at the discretion of the study Investigator. Subjects who remain on their current ART regimen must show confirmed HIV-1 RNA levels ≤5000 copies/mL before resuming study drug dosing at the discretion of the Investigator.

6.9.2. Management of Subjects during ATI CCI [redacted]

Subjects will discontinue ART on ATI Visit 1 (Beginning of **analytical treatment interruption**) through ATI Visit 24. CCI [redacted]

Subjects will be closely observed for the initial 24 week ATI period during which plasma HIV-1 RNA values, CD4+ count, CD8 cell count, CD4/CD8 ratio and CD4 % will be measured once a week. CCI [redacted]

During the 24 week ATI period (ATI Visits 1-24) CCI [redacted], ART will be re-initiated if subject meets the criteria as defined in Section 6.6.1.

If/when HIV-1 RNA is > 1,000 copies/mL during the ATI CCI [redacted], resistance testing will be performed at the next visit. Subject will be monitored and HIV-1 RNA viral load will be measured at subsequent visits.

6.9.3. Management of Virologic Failure post ART Restart

If a subject's ART has to be re-initiated, subject's viral load will be checked on weekly basis. If after 4 weeks post ART re-initiation, HIV-1 viral load remains ≥ 200 copies/mL, resistance testing will be performed. If primary resistance mutations to the subject's existing ART regimen are identified, a new ART regimen will be configured at the discretion of the Investigator.
If the genotyping/phenotyping assay fails to provide results or no drug resistance mutations are identified, a new ART regimen may be configured at the discretion of the Investigator.

6.10. Management of HIV-1 Seronegative Study Subject Sexual Partners

In addition to requiring utilization of barrier prophylaxis by all study subjects, HIV-1 seronegative sexual partners of enrolled study subjects may be referred to a local HIV Pre-Exposure Prophylaxis (PrEP) clinic for HIV risk assessment evaluation.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

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

7.1.1. Adverse Events

An adverse event (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, lack of efficacy, 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.
- Pre-existing 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 pre-existing and should be documented on the medical history CRF.

7.1.2. Serious Adverse Events

A **serious adverse event** (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.

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

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to IMP interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, 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 (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

For specific information on handling of clinical laboratory abnormalities in this study, please refer to Section 7.5.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified sub-investigator 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 sub-investigator is responsible for assessing the relationship to IMP or current ART using clinical judgment and the following considerations:

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

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

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

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

7.2.2. Assessment of Severity

The severity grading of AEs will be assessed as Grade 1, 2, 3, or 4 using the GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 4). 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.

7.3. 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 case report form (CRF/eCRF): all SAEs and adverse events related to protocol-mandated procedures.

Adverse Events

Following initiation of study medication, all AEs, regardless of cause or relationship, and throughout the duration of the study, including the protocol-required post-treatment follow-up period must be reported to the eCRF database as instructed.

All AEs should be followed up until resolution or until the adverse event is stable, if possible. Gilead Sciences may request that certain AEs be followed beyond the protocol defined follow up period.

Serious Adverse Events

All SAEs, regardless of cause or relationship, that occurs after the subject first consents to participate in the study (ie, 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 Pharmacovigilance and Epidemiology (PVE) as instructed.
This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

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.

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, ie, 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:

  Gilead Sciences PVE Representative: 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.
- All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline.
- 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 onto 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 investigator's brochure 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 (eg, clinical chemistry, hematology, 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 (eg, electrocardiogram, 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 (ie, anemia) not the laboratory result (ie, decreased hemoglobin).

Severity should be recorded and graded according to the GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 4) 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.

7.6. Toxicity Management

7.6.1. Management of Dose-Limiting Toxicities (DLTs)

Prior to the subject being administered the in-clinic dose the Investigator will verify the subjects continued eligibility for dosing, including the absence of DLTs listed below:

- ALT elevation as defined as:
  - — ALT ≥ 10 × ULN **OR**
  - — Confirmed ALT elevation (ie. Grade shift or 2× previous value) with evidence of worsened hepatic function (e.g. total bilirubin > 2mg/dL above Baseline, serum albumin > 1 g/dL decrease from Baseline)
- A confirmed ≥ Grade 3 AE considered drug related by the Investigator
- A confirmed, clinically significant ≥ Grade 3 laboratory abnormality considered study drug-related by the investigator

- A persistent (≥ 72 hours) ≥ Grade 2 flu-like symptom (pyrexia, fatigue, myalgia, arthralgia, headache, chills) considered study drug-related by the investigator

- A post-dose increase in plasma HIV-1 RNA that fails to resolve to < 5000 copies/mL within two re-test measurements

The designated Safety Evaluation Committee contact will be notified within 24 hours of the Investigator's knowledge of a subject having any of the above DLTs. Dosing must be withheld until the Safety Evaluation Committee determines the appropriate next steps, including but not limited to additional safety, pharmacokinetic and pharmacodynamic assessments.

The SEC may hold or discontinue study drug dosing for a subject if they receive GS-9620 and experience one or more DLTs. The SEC may also suspend dosing in additional subjects.

7.6.2. Management of Other Toxicities

Unless otherwise specified in Section 7.6.1, toxicities will be managed according to the guidelines below.

- All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in Appendix 3.

- Grade 3 and 4 clinically significant laboratory abnormalities should be confirmed by repeat testing within 3 calendar days of receipt of results and before investigational medicinal product (IMP) discontinuation, unless such a delay is not consistent with good medical practice.

- Clinical events and clinically significant laboratory abnormalities will be graded according to the Table for GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 4).

- When restarting IMP following resolution of the adverse event, the investigational medicinal product should be restarted at full dose or modified dose that is dependent upon discussion with the Gilead Sciences Medical Monitor.

- Any recurrence of the Grade 3 or 4 clinical or clinically significant laboratory adverse event following dose interruption mandates permanent discontinuation of IMP.

- Any questions regarding toxicity management should be directed to the Gilead Sciences Medical Monitor.

7.6.2.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

Continue investigational medicinal product at the discretion of the Investigator.

7.6.2.2. Grade 3 Laboratory Abnormality or Clinical Event

- For a Grade 3 clinical event or clinically significant Grade 3 laboratory abnormality confirmed by repeat testing, IMP should be withheld until the toxicity returns to ≤ Grade 2.
- If a laboratory abnormality recurs to ≥ Grade 3 following rechallenge with IMP, then IMP should be permanently discontinued and the subject managed according to local practice.

7.6.2.3. Grade 4 Laboratory Abnormality or Clinical Event

- For a Grade 4 clinical event or clinically significant Grade 4 laboratory abnormality confirmed by repeat testing, IMP should be withheld until the toxicity returns to ≤ Grade 2.
- 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 (and therefore not an AE), Grade 4 laboratory abnormality (eg, Grade 4 CK after strenuous exercise, or triglyceride elevation that is non-fasting or that can be medically managed).

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 occupational exposure and product complaints as well as adverse events in an infant following exposure from breastfeeding, and pregnancy reports regardless of an associated AE.

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 complaints 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 below 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 (eg, 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 Sections 7.1.1 and 7.1.2. 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 .

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to or Gilead PVE using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the subject should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE, fax number PPD or email PPD

Refer to Appendix 5 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 does 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 this study is:

- To evaluate the safety and tolerability of a 10-dose regimen of GS-9620 in HIV-1 infected controllers on ART and during ATI following GS-9620 dosing

The secondary objectives of this study are:

Virology

- To evaluate the effect of GS-9620 in reactivating the HIV-1 reservoir, as measured by changes in plasma HIV-1 RNA by Taqman 2.0
- To evaluate the effect of GS-9620 in modulating time to virologic rebound and plasma viral set-point following ATI

Immunology/Pharmacodynamics

- To evaluate the PD of GS-9620 as measured by changes in serum/plasma cytokines, and mRNA of ISGs in whole blood
- To evaluate effects of GS-9620 on immune cell activation in whole blood

Pharmacokinetics

- To evaluate the plasma PK of GS-9620

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[redacted]

8.1.2. Primary Endpoint

The primary endpoint is incidence of treatment-emergent SAEs and all treatment-emergent adverse events.

8.1.3. Secondary Endpoint

The secondary endpoints of this study are:

Virology

- Changes in plasma HIV-1 RNA by Taqman 2.0
- Time to virologic rebound and change in plasma viral load set-point following ATI
- Peak HIV-1 viral load during ATI

Immunology/Pharmacodynamics

- Changes in serum/plasma cytokines and mRNA of ISGs in whole blood
- Changes in immune cell activation in whole blood

Pharmacokinetics

- PK parameters of GS-9620 in plasma

CCI [redacted]

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. All Randomized

The randomized analysis set includes all subjects who are randomized into the study. This is the primary analysis set for by-subject listings.

8.2.1.2. Efficacy

8.2.1.2.1. Full Analysis Set

The full analysis set (FAS) will include all subjects who (1) are randomized into the study and (2) have received at least one dose of study drug. Subjects with major eligibility violations that are identifiable based on pre-randomization characteristics will be excluded.

Subjects will be grouped according to the treatment to which they were randomized.

8.2.1.3. Safety

The safety analysis set will include all randomized subjects who received at least one dose of study drug. All the data collected up to 30 days after subjects permanently discontinue their study drug will be included in the safety summaries. Subjects will be grouped according to the treatment they actually received.

8.2.1.4. Phamacokinetics

The GS-9620 PK analysis set will include all subjects who are randomized and have received at least one dose of study drug and for whom PK parameters of analyte GS-9620 are available.

8.3. Data Handling Conventions

Natural logarithm transformation for key PK parameters, such as C_{max}, C_{tau} and AUC_{tau}, will be applied for pharmacokinetic analysis, as appropriate.

For summary statistics, PK concentration values below the limit of quantitation (BLQ) will be imputed as zero at predose and one-half the lower limit of quantitation (LLOQ) at post dose, where LLOQ is corrected for the dilution factor (ie, reported dilution/dilution factor). Individual values that are BLQ will be presented as "BLQ" in the concentration data listing and will be imputed as specified above for summary purpose.

8.4. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized using standard descriptive methods by treatment group.

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

Baseline data including body weight, height, body mass index, HIV-1 infection will be summarized.

8.5. Efficacy Analysis

The efficacy analysis will be based on the full analysis set (FAS).

8.5.1. Virology Analysis

The change in plasma HIV-1 RNA by Taqman 2.0 will be summarized by treatment group.

The incidence of detectable plasma HIV-1 RNA by Taqman 2.0 at each visit will be summarized by treatment group.

Time to viral rebound will be summarized by treatment group.

The difference in plasma viral set point between pre-ART value and prior to ART re-initiation will be summarized by treatment group.

The peak HIV-1 viral load during ATI will also be summarized by treatment group.

8.5.2. Immunology/Pharmacodynamics Analysis

The changes in serum/plasma cytokines, mRNA of ISGs in whole blood, and cell activation in whole blood will be summarized using descriptive statistics by treatment group.

8.6. Safety Analysis

All safety analyses will be performed using the safety analysis set.

All safety data collected on or after the date that study drug was first taken up to the date of last dose of study drug plus 30 days will be summarized by treatment group according to the study drug received. Data for the pretreatment period and the period post the date of last dose of study drug plus 30 days will be included in data listings.

8.6.1. Extent of Exposure

A subject's extent of exposure to study drug will be generated from the study drug administration data. Exposure data will be summarized by treatment group.

Duration of exposure to study drug will be expressed as the number of weeks between the first and last dose of the study drug, inclusive, regardless of temporary interruptions in study drug administration and summarized by treatment.

Dosing information for individual subjects will be listed.

8.6.2. Adverse Events

Clinical and laboratory adverse events will be coded using the Medical Dictionary for Regulatory Activities (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 adverse event will be defined as any adverse event 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 adverse event leading to study drug discontinuation.

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

On an ongoing basis adverse events will be reviewed for events that might meet the definition of Stage 3 Opportunistic Illnesses in HIV are indicative of an AIDS-Defining Diagnoses. The Gilead medical personnel will review the possible Stage 3 events and approve the events that meet the definition. Those events that do meet the Stage 3 Opportunistic Illness definition of an AIDS-Defining Diagnosis will be listed.

A listing of Stage 3 Opportunistic Illnesses in HIV 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 4.

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least one toxicity grade from baseline at any time post baseline up to and including the date of last dose of study drug plus 30 days, will be summarized by treatment group. If baseline data are missing, 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 drug or after the subject has been discontinued from treatment plus 30 days will be included in a data listing.

8.7. Pharmacokinetic Analysis

The concentration data of GS-9620 will be summarized by nominal sampling time using descriptive statistics. For GS-9620, pharmacokinetic parameters (C_{max}, T_{max}, C_{last}, T_{last}, λz, AUC_{inf}, AUC_{last}, and $t_{½}$) will be listed and summarized using descriptive statistics (e.g., sample size, arithmetic mean, geometric mean, coefficient of variation (%), standard deviation, median, minimum, and maximum). Plasma concentrations over time will be plotted in semi-logarithmic and linear formats as mean ± standard deviation, and median (Q1, Q3).

8.8. Sample Size

This is an exploratory study to characterize the safety and efficacy of GS-9620; therefore, no power calculation was performed. Sample size is determined based on empirical considerations. A total of up to 20 subjects receiving GS-9620 will provide a preliminary assessment of safety and efficacy.

8.9. Safety Evaluation Committee

A Safety Evaluation Committee (SEC) will review study progress, virology and safety of enrolled subjects. The SEC will consist of members not directly involved with the conduct of the study. After half of the subjects have received four doses of GS-9620 or placebo-to-match, the SEC will review safety data, including adverse events, clinical laboratory results, and plasma HIV-1 RNA. Please refer to the SEC Charter for additional details.

8.10. Analysis Schedule

8.10.1. Interim Unblinded Analyses

Prior to the final analysis, a few selected individuals from Gilead will be unblinded to assess the interim safety and virology data of GS-9620. The immunology/pharmacodynamics and PK data of GS-9620 may also be part of the unblinded assessment. This group may consist of at least one representative from Clinical Research, Biostatistics, Clinical Pharmacology, Pharmacovigilance/Epidemiology, Biomarkers, Clinical Virology and may include other personnel as necessary. Details of unblinding (eg, memberships, responsibilities, analysis schedules) will be defined in a charter.

After at least 10 subjects complete ATI Week 24 or meet criteria to restart ARV, the Sponsor will conduct interim unblinded analyses to review the data as described above. The results from these analyses may be submitted to regulatory agencies to facilitate the clinical development program, presented externally or published to disseminate the findings.

8.10.2. Final Analyses

The Sponsor will conduct a final analysis of all data after the last subject in the study completes the last visit or prematurely discontinues from 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 Good Clinical Practice Directive 2005/28/EC.

The investigator will ensure adherence to the basic principles of Good Clinical Practice, as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998.

The investigator and all applicable subinvestigators will comply with 21 CFR, Part 54, 1998, 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 an IRB/IEC. The investigator will not begin any study subject activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB/IEC 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 IRB or IEC 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 IRB/IEC or local requirements. CCI [redacted]

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, IRB/IEC, 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 investigator brochure, 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, IRB/IEC 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, ie, 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 adverse events 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 coordinator 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 IRB/IEC, 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 must submit all protocol modifications to the IRB/IEC in accordance with local requirements and receive documented IRB/IEC approval 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.

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

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11. APPENDICES

Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGEMENT

A Phase 1b, Randomized, Double-Blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of GS-9620 in Antiretroviral Treated HIV-1 Infected Controllers

GS-US-382-3961, Amendment 3, 05 February 2019

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

PPD

Name (Printed)
Author

PPD

Feb. 5, 2019
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

			Period 1[v,w]																										P2 P=Period			P3		P2 or P3		
Visit	**Screening [a]**	**Day -13**	**Dose 1 -Day 1**	**Dose 1-Day 2**	**Dose 1-Day 8**	**Dose 2- Day 1**	**Dose 2-Day 8**	**Dose 3 Day 1**	**Dose 3-Day 8**	**Dose 4 Day 1**	**Dose 4-Day 2**	**Dose 4-Day 4**	**Dose 4-Day 8**	**Dose 5 Day 1**	**Dose 5-Day 8**	**Dose 6 Day 1**	**Dose 6-Day 4**	**Dose 6-Day 8**	**Dose 7 Day 1**	**Dose 7-Day 8**	**Dose 8 Day 1**	**Dose 8-Day 8**	**Dose 9 Day 1**	**Dose 9-Day 8**	**Dose 10 Day 1**	**Dose 10-Day 2**	**Dose 10-Day 4**	**Dose 10-Day 8**	**Dose 10-Day 14**	**ATI Visit 1[p]**	**Visits 2-24[q,x]**	**ATI Remission [r]**	CCI	**End of Study[t]**	**ART Re-initiation Visits[x]**	**Post ART re-suppression Visits 1-6[z]**	**ESDD[u]**
Informed Consent	X																																			
Medical History[b]	X	X	X																																	
Pre-ART viral load set point	X																																			
HLA Class I and II type , pre-ART CD4 Nadir, historical genotype	X																																			
AE and Con Meds[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Exam	X																												X	X h	X					
Symptom Directed Physical Exam		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X i			X		X	X
12-Lead ECG	X																																			
Vital Signs	X		X			X		X		X				X		X			X		X		X		X				X	X j	X		X	X	X	X
Weight	X		X			X		X		X				X		X			X		X		X		X				X	X j	X		X		X	X
Height	X																																			

			Period 1[v,w]																									P2 P=Period			P3		P2 or P3		
Visit	**Screening [a]**	**Day -13**	**Dose 1 -Day 1**	**Dose 1-Day 2**	**Dose 1-Day 8**	**Dose 2- Day 1**	**Dose 2-Day 8**	**Dose 3 Day 1**	**Dose 3-Day 8**	**Dose 4 Day 1**	**Dose 4-Day 2**	**Dose 4-Day 4**	**Dose 4-Day 8**	**Dose 5 Day 1**	**Dose 5-Day 8**	**Dose 6 Day 1**	**Dose 6-Day 4**	**Dose 6-Day 8**	**Dose 7 Day 1**	**Dose 7-Day 8**	**Dose 8 Day 1**	**Dose 8-Day 8**	**Dose 9 Day 1**	**Dose 9-Day 8**	**Dose 10 Day 1**	**Dose 10-Day 2**	**Dose 10-Day 4**	**Dose 10-Day 8**	**Dose 10-Day 14**	**ATI Visit 1[p]**	**Visits 2-24[q,x]**	**ATI Remission [r]**	CCI	**End of Study[t]**	**ART Re-initiation Visits[x]**	**Post ART re-suppression Visits 1-6[z]**	**ESDD[u]**
Review of I/E criteria[c]		X																																	
Randomization		X																																	
CCI																																			
Urine Collection for																																			
Urinalysis	X		X			X		X		X				X		X			X		X		X		X				X	X[k]			X		X	X
Urine Pregnancy Test[d]			X			X		X		X				X		X			X		X		X		X			X	X	X[1]	X		X	X[l]	X	X
Blood collection for																																			
Chemistry	X		X			X		X		X				X		X			X		X		X		X				X	X[k]			X		X	X
Hematology	X		X			X		X		X				X		X			X		X		X		X				X	X[k]			X		X	X
Metabolic assessment[e]	X																																	X			
eGFR	X		X																											X	X[k]			X			X

			Period 1[v,w]																										P2 P=Period			P3		P2 or P3		
Visit	**Screening [a]**	**Day -13**	**Dose 1 -Day 1**	**Dose 1-Day 2**	**Dose 1-Day 8**	**Dose 2- Day 1**	**Dose 2-Day 8**	**Dose 3 Day 1**	**Dose 3-Day 8**	**Dose 4 Day 1**	**Dose 4-Day 2**	**Dose 4-Day 4**	**Dose 4-Day 8**	**Dose 5 Day 1**	**Dose 5-Day 8**	**Dose 6 Day 1**	**Dose 6-Day 4**	**Dose 6-Day 8**	**Dose 7 Day 1**	**Dose 7-Day 8**	**Dose 8 Day 1**	**Dose 8-Day 8**	**Dose 9 Day 1**	**Dose 9-Day 8**	**Dose 10 Day 1**	**Dose 10-Day 2**	**Dose 10-Day 4**	**Dose 10-Day 8**	**Dose 10-Day 14**	**ATI Visit 1[p]**	**Visits 2-24[q,x]**	**ATI Remission [r]**	CCI	**End of Study[t]**	**ART Re-initiation Visits[x]**	**Post ART re-suppression Visits 1-6[z]**	**ESDD[u]**
Serum Pregnancy Test[d]	X																																		
CD4+ cell count, CD8 + cell count, CD4/CD8 ratio and CD4 %	X		X			X		X		X				X		X			X		X		X		X				X	X	X		X	X	X	X
HBV/HCV Serology[f]	X																																		
GS-9620 Intensive PK[g]			X	X																															
Plasma ART PK	X																X													X cc					
TLR7 genotyping		X																																	
Plasma HIV-1 RNA by Taqman 2.0	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X
HIV -1 Genotype/Phenotype[bb]																																			
VAS Questionnaire			X							X											X															
Plasma HIV-1 RNA by SCA		X								X	X	X				X	X								X	X	X		X			X			X aa	

			Period 1[v,w]																										P2 P=Period			P3	P2 or P3		
Visit	Screening [a]	Day -13	Dose 1 -Day 1	Dose 1-Day 2	Dose 1-Day 8	Dose 2- Day 1	Dose 2-Day 8	Dose 3 Day 1	Dose 3-Day 8	Dose 4 Day 1	Dose 4-Day 2	Dose 4-Day 4	Dose 4-Day 8	Dose 5 Day 1	Dose 5-Day 8	Dose 6 Day 1	Dose 6-Day 4	Dose 6-Day 8	Dose 7 Day 1	Dose 7-Day 8	Dose 8 Day 1	Dose 8-Day 8	Dose 9 Day 1	Dose 9-Day 8	Dose 10 Day 1	Dose 10-Day 2	Dose 10-Day 4	Dose 10-Day 8	Dose 10-Day 14	ATI Visit 1[p]	Visits 2-24[q,x]	ATI Remission [r]	CCI	End of Study[t]	ART Re-initiation Visits[x]	Post ART re-suppression Visits 1-6[z]	ESDD[u]
PBMC Associated viral RNA & DNA by CAVR/CAVD		X								X	X	X				X	X							X	X	X		X			X			X[aa]	
CCI																																			
CCI																																			
Whole blood ISG mRNA			X	X						X	X													X	X										X
Cytokines, chemokines			X	X	X					X	X		X											X	X		X				X				X
T cell ICS		X																										X			X				
Immune cell activation, phenotyping		X								X	X																	X			X				
Serum antibody profiling assays		X																										X			X				
CCI																																			
CCI																																			

Visit	Screening [a]	Day -13	Period 1 [v,w] Dose 1 -Day 1	Dose 1-Day 2	Dose 1-Day 8	Dose 2- Day 1	Dose 2-Day 8	Dose 3 Day 1	Dose 3-Day 8	Dose 4 Day 1	Dose 4-Day 2	Dose 4-Day 4	Dose 4-Day 8	Dose 5 Day 1	Dose 5-Day 8	Dose 6 Day 1	Dose 6-Day 4	Dose 6-Day 8	Dose 7 Day 1	Dose 7-Day 8	Dose 8 Day 1	Dose 8-Day 8	Dose 9 Day 1	Dose 9-Day 8	Dose 10 Day 1	Dose 10-Day 2	Dose 10-Day 4	Dose 10-Day 8	Dose 10-Day 14	P2 P=Period ATI Visit 1 [p]	Visits 2-24 [q,x]	ATI Remission [r]	P3 CCI End of Study [t]	P2 or P3 ART Re-initiation Visits [x]	Post ART re-suppression Visits 1-6 [z]	ESDD [u]
CCI																																			
Review of DLTs						X		X		X				X		X			X		X		X		X										
In-Clinic Dosing [y]			X			X		X		X				X		X			X		X		X		X										

a Evaluations to be completed within 35 days prior to Pre-Baseline/Day -13
b Medical history including route and estimated duration of HIV-1 infection, history of HIV-1 disease-related events, anti-retroviral treatment (ART) history for at least 6 months and prior medications within 35 days of the screening visit
c If subject's ART regimen is changed ≥ 45 days prior to Baseline/Dose 1-Day 1, plasma HIV-1 RNA <50 copies/mL at Pre-baseline/Day -13 visit is required to confirm eligibility.
d Females of childbearing potential only. Positive urine pregnancy tests will be confirmed with a serum test.
e Fasting (no food or drinks, except water, at least 8 hours prior to blood collection) glucose and lipid panel (total cholesterol, HDL, direct LDL, triglycerides). 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.
f HBV blood panel will be performed at Screening (Hepatitis B virus surface antigen (HBsAg), Hepatitis B virus surface antibody (HBsAb) and Hepatitis B virus core antibody (HBcAb)). Hepatitis C antibody (HCVAb) will be performed.
g Intensive PK samples will be collected at Pre-dose (≤ 5 minutes prior to dosing), 0.5, 1, 2, 4, 6, 8, 10 and 24 hours post dose at Dose 1-Day 1 visit.
h Complete physical examination at visits 5, 9,13,17, 21, 26, 28, 30, 32, 34, 36
i Symptom directed physical examination as needed at visits 3, 7, 11, 15, 19, 23, 25, 27, 29, 31, 33, 35
j Vital signs and weight at visits 3,5,7,9,11,13,15,17,19,21,23.

k Chemistry, Hematology, eGFR and Urinalysis at visits 5, 9, 13, 17, 21, 26, 28, 30, 32, 34, 36

l Urine pregnancy test at visits 3,5,7,9,11,13,15,17,19,21,23. Urine pregnancy test will also be done at first ART re-initiation visit and monthly thereafter until Post ART re-suppression Visits

[redacted]

o Any adverse event 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, or is otherwise explained.

p ATI Visit 1 to occur at Dose 10-Day 28 for subjects with HIV-1 RNA <50 copies/mL at Dose 10-Day 14 visit. For subjects with viral load >50 copies/mL at Dose 10-Day 14, the ATI Visit 1will only occur if undetectable viral load is achieved within two re-test measurements. Subjects to discontinue study medication and ART from ATI Visit 1 through ATI Visit 24 CCI .

q Weekly visits 2-24

r This visit will be planned after completion of 12 weeks of ATI for subjects with plasma HIV-1 RNA <50 copies/mL in the absence of ART re initiation. If subjects have HIV-1 viral load <50 copies/mL at ATI Visit 12, the visit should occur within a week of ATI Visit 12. However, if the subject does not have HIV-1 viral load <50 copies/mL at ATI Visit 12, this visit may still occur at a later time point between ATI Visit 13 CCI once the HIV-1 viral load <50 copies/mL.

[redacted]

t End of study visit to occur 7 days (± 1 day) after the last ATI Visit if subject has not re-initiated ART during Period 2 and 3.

u Early Study Drugs Discontinuation visit is required if subject discontinues study medication prior to completion of Dose 10. The visit to occur within 30 days of last dose of study drug.

v If HIV-1 RNA viral load will be >5000 copies/mL at any visit post Dose, viral load will be observed at next scheduled visit or retested within 4 days. The next dose will be withheld and only given if viral load of ≤5000 copies/mL is achieved. The study procedure schedule will be reset relative to the next dose of GS-9620.

w If plasma virus HIV-1 RNA levels are > 5000 copies/mL at third retest visit during a single dosing period, then this subject will be considered to have confirmed virologic failure and blood samples from this visit will be used for HIV-1 genotype/phenotype testing with assays corresponding to the antiretroviral medications the subject is taking.

x During Visits 2-24 in Period 2 CCI , ART will be re-initiated if subject meets the criteria defined in Section 6.6.1. Once ART is re-initiated, weekly visits (ART Re-initiation visits) will occur to measure plasma viral load and CD4+ count will be conducted until plasma viral load becomes undetectable (<50 copies/mL), and then every other week until two consecutive measures are undetectable.

y Dosing to occur in fasting state. Food not permitted 2 hours prior to and 2 hours after dosing. Overnight fasting is preferable. Aside from 240 mL water provided at dosing, water/liquid not to be permitted from 1 hour prior to until 2 hours after dosing. Subjects to provide information on food consumption and total fasting time prior to dosing.

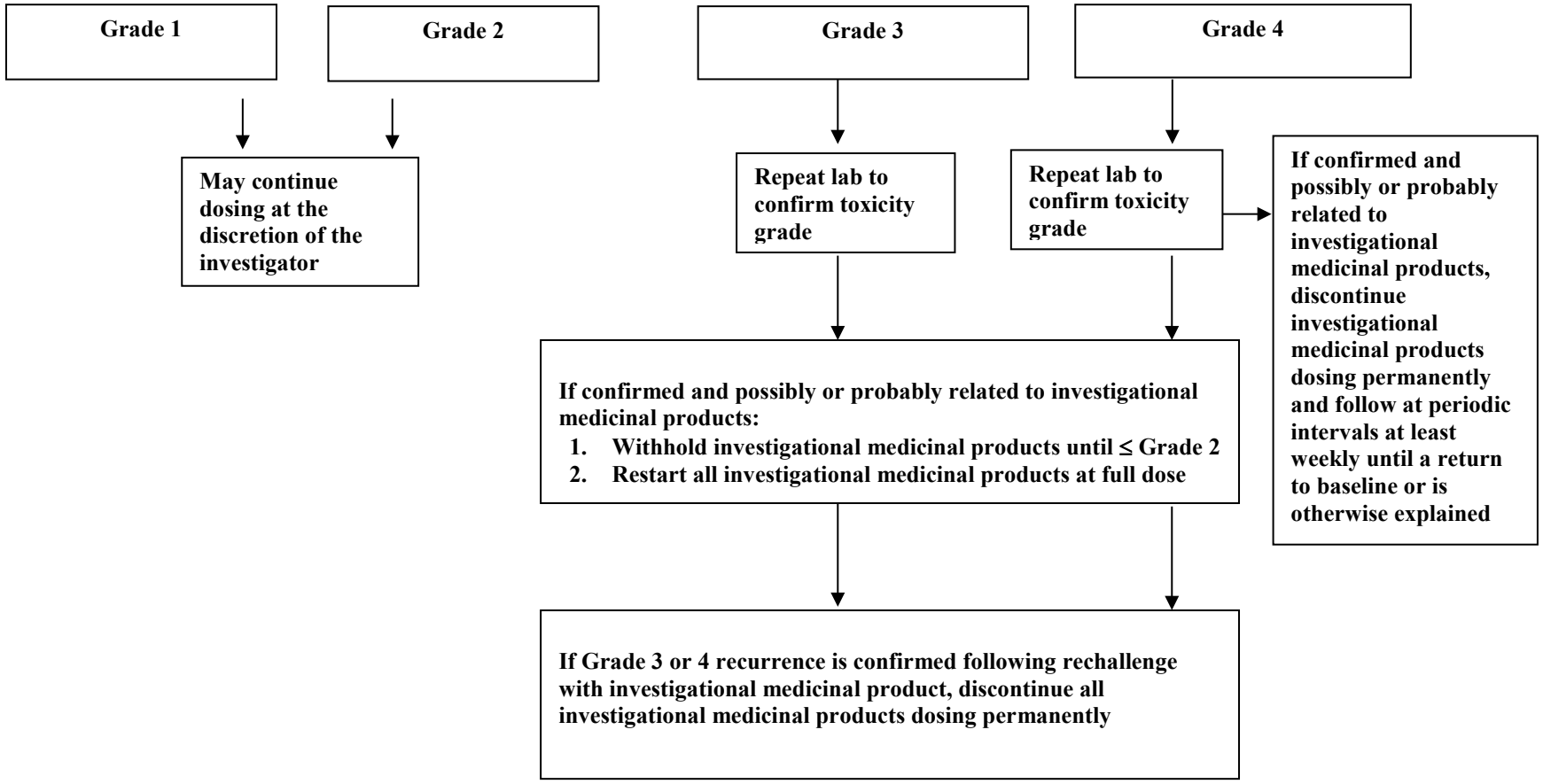
z Post ART Re-suppression visits is applicable for subject(s) who re-initiates ART during ATI. The visit to occur monthly for six months after subject has achieved HIV-1 RNA of <50 copies/mL at two consecutive visits. A window of ± 6 days may be used to schedule this visit

aa To be performed at Post ART Re-suppression Visit 6 only

bb HIV-1 genotype and phenotype testing for subjects with prolonged Viremia. Refer to Section 6.9 for retesting and subject management.

cc Additional PK samples may be drawn to verify that subject continues being off-ART during the ATI phase (Period 2 CCI). Samples will be drawn upon Sponsor request depending on the subject's HIV-1 RNA levels

Appendix 3. Management of Clinical and Laboratory Adverse Events



Appendix 4. 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** HIV NEGATIVE **Adult and Pediatric ≥ 57 days**	8.5 to 10.0 g/dL 85 to 100 g/L 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	7.5 to < 8.5 g/dL 75 to < 85 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	6.5 to < 7.5 g/dL 65 to < 75 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	< 6.5 g/dL < 65 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
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

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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** **Infant <1 Year**	3.0 to <LLN mEq/L 3.0 to <LLN mmol/L 3.0 to 3.4 mEq/L 3.0 to 3.4 mmol/L	2.5 to < 3.0 mEq/L 2.5 to < 3.0 mmol/L 2.5 to < 3.0 mEq/L 2.5 to <3.0 mmolL	2.0 to < 2.5 mEq/L 2.0 to < 2.5 mmol/L 2.0 to < 2.5 mEq/L 2.0 to <2.5 mmolL	< 2.0 mEq/L < 2.0 mmol/L < 2.0 mEq/L <2.0 mmolL
Hyperkalemia **Adult and Pediatric ≥ 1 Year** **Infant <1 Year**	5.6 to 6.0 mEq/L 5.6 to 6.0 mmol/L >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 > 6.0 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 > 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L > 7.0 mEq/L > 7.0 mmol/L
Hypoglycemia **Adult and Pediatric ≥ 1 Month** **Infant, < 1 Month**	55 to 64 mg/dL 3.03 to 3.58 mmol/L 50 to 54 mg/dL 2.8 to 3.0 mmol/L	40 to < 55 mg/dL 2.20 to < 3.03 mmol/L 40 to < 50 mg/dL 2.2 to < 2.8 mmol/L	30 to < 40 mg/dL 1.64 to < 2.20 mmol/L 30 to < 40 mg/dL 1.7 to < 2.2 mmol/L	< 30 mg/dL < 1.64 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** **Infant < 1 Year**	1.5 mg/dL to < LLN 87 µmol/L to < LLN N/A	1.0 to < 1.5 mg/dL 57 to < 87 µmol/L 1.0 mg/dl to <LLN- 57 µmol to <LLN	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L 0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 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) **Pediatric < 18 Years**	200 to 239 mg/dL 5.16 to 6.19 mmol/L 170 to 199 mg/dL 4.39 to 5.15 mmol/L	> 239 to 300 mg/dL > 6.19 to 7.77 mmol/L > 199 to 300 mg/dL > 5.15 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L > 300 mg/dL > 7.77 mmol/L	NA 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** **≥ 16 years**	- 3.0 g/dL to < LLN 30 g/L to < LLN	2.0 to < LLN g/dL 20 to < LLN g/L 2.0 to < 3.0 g/dL 20 to < 30 g/L	< 2.0 g/dL < 20 g/L < 2.0 g/dL < 20 g/L	NA NA

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) **Pediatric ≤ 17 Years** (with repeat testing at same visit)	140–159 mmHg systolic OR 90–99 mmHg diastolic NA	> 159–179 mmHg systolic OR > 99–109 mmHg diastolic 91st–94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	> 179 mmHg systolic OR > 109 mmHg diastolic ≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization (other than ER visit) indicated 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
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

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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** **Pediatric < 1 Year**	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline/24 hr Liquid stools (more unformed than usual) but usual number of stools	Persistent episodes of unformed to watery stools OR Increase of 4–6 stools over baseline per 24 hrs. Liquid stools with increased number of stools OR Mild dehydration	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated Liquid stools with moderate dehydration	Life-threatening consequences (eg, hypotensive shock) 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
Developmental delay – **Pediatric ≤ 16 Years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than ER visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social/functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular Weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizure: (new onset)	NA	1 seizure	2–4 seizures	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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 5. 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.

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

b. Definition of Male Fertility

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

2) Contraception Requirements for Female Subjects

a. Study Drug Effects on Pregnancy and Hormonal Contraception

The risks of treatment with GS-9620 during pregnancy have not been evaluated in humans.

A clinical pharmacokinetic study evaluating the drug interaction potential of GS-9620 has not been conducted, however, based on the non-overlapping metabolic pathways for GS-9620 and oral contraceptives, no clinically relevant drug interactions are expected upon co-administration of these agents. As such, the efficacy of oral contraceptives is not expected to be affected by GS-9620.

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 have a negative serum pregnancy test at Screening and a negative pregnancy test on the Pre-Baseline/Day -13 visit prior to randomization. At minimum, a pregnancy test will be performed at each dosing visit. 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 also agree to one of the following from Screening until 36 days following the last dose of study drug.

- 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 female or male condom without spermicide plus one of the following methods of birth control listed below.
- Intrauterine device (IUD) with a failure rate of <1% per year
- Intrauterine hormone-releasing system (IUS) 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)
- Oral contraceptives (either combined or progesterone only)
- Injectable progesterone
- Implants of levonorgestrel
- Transdermal contraceptive patch
- Contraceptive vaginal ring

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) Contraception Requirements for Male Subjects

It is theoretically possible that a relevant systemic concentration may be achieved in a female partner from exposure of the male subject's seminal fluid. Therefore, male subjects with female partners of childbearing potential must use condoms during treatment and until 90 days after the last dose. Additional contraception recommendations should also be considered if the female partner is not pregnant.

Male subjects must also refrain from sperm donation during treatment and until at least 90 days after the last dose.

4) 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.

5) 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 (or 90 days for female partners of male subjects) 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. Subjects whose partner has become pregnant or suspects she is pregnant during the study must report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.7.2.1.

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}