CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2/3 Multicenter, Open-Label, Multicohort, Two-Part Study Evaluating the Pharmacokinetics (PK), Safety, and Antiviral Activity of Elvitegravir (EVG) Administered with a Background Regimen (BR) Containing a Ritonavir-Boosted Protease Inhibitor (PI/r) in HIV-1 Infected, Antiretroviral Treatment-Experienced Pediatric Subjects
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Dr. Foster City, CA 94404
IND Number:	072177
EudraCT Number:	2013-001969-16
Clinical Trials.gov Identifier:	TBD
Indication:	HIV-1
Protocol ID:	GS-US-183-0160
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CONFIDENTIALITY STATEMENT

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PROTOCOL SYNOPSIS

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

Study Title:	A Phase 2/3 Multicenter, Open-Label, Multicohort, Two-Part Study Evaluating the Pharmacokinetics (PK), Safety, and Antiviral Activity of Elvitegravir (EVG) Administered with a Background Regimen (BR) Containing a Ritonavir-Boosted Protease Inhibitor (PI/r) in HIV-1 Infected, Antiretroviral Treatment-Experienced Pediatric Subjects
IND Number:	072177
EudraCT Number:	2013-001969-16
Clinical Trials.gov Identifier:	TBD
Study Centers Planned:	Approximately 50 centers in North America, Europe, Latin America, Asia Pacific, and Africa
Objectives:	The primary objectives of this study are as follows: • To evaluate the steady-state PK and confirm the dose of ritonavir-boosted elvitegravir (EVG/r) in HIV-1 infected, antiretroviral treatment-experienced subjects 4 weeks to <18 years of age • To evaluate the safety and tolerability of EVG/r in HIV-1 infected, antiretroviral treatment-experienced subjects 4 weeks to <18 years of age The secondary objective of this study is as follows: • To evaluate the antiviral activity of EVG/r in HIV-1 infected, antiretroviral treatment-experienced subjects 4 weeks to <18 years of age who are failing their current HAART regimen
Study Design:	Open-label, multicohort, two-part study evaluating the PK, safety, and antiviral activity of EVG administered with a BR containing a PI/r in HIV-1 infected, antiretroviral treatment-experienced pediatric subjects. Up to approximately 86 pediatric subjects 4 weeks to <18 years of age will be enrolled as follows:

Part A

Approximately 36 subjects either with suppressed viremia (HIV-1 <50 copies/mL) or failing a current antiretroviral regimen (HIV-1 RNA >1,000 copies/mL) will be enrolled to evaluate the steady state PK and confirm the dose of EVG. Only subjects aged 4 weeks to < 12 years old will be enrolled in Part A.

For subjects with HIV-1 RNA <50 copies/mL at screening, EVG will be added to the existing BR that must include a PI/r. The dose of EVG will be dependent upon the coadministered PI/r and will be based on body weight.

For subjects with HIV-1 RNA >1,000 copies/mL at screening, EVG will be added to a newly constructed BR selected by the investigator that is based on the subject's antiretroviral history and screening or historical viral resistance results. The BR must include at least 2 fully-active agents, one of which is a fully-active PI/r (fully-active PI/r is defined by genotypic analysis).

The PI/r contained in the BR must be one of the following: lopinavir/r (Kaletra), atazanavir/r, darunavir/r, tipranavir/r, or fosamprenavir/r. For subjects < 2 months old, only lopinavir/r is allowed. The BR may contain additional antiretrovirals except for the following: saquinavir, indinavir, nelfinavir, double PI regimens, efavirenz, nevirapine, delavirdine or an integrase strand transfer inhibitor. All PI should be administered according to local product label.

All subjects will take their ritonavir dose based on the dosing schedule prescribed for the PI; no additional ritonavir is required to be taken with EVG.

Subjects will be enrolled sequentially by cohort* as follows:

- **Cohort 2:** 6 to < 12 years old (n ≥ 12)
- **Cohort 3:** 2 to < 6 years old (n ≥12)
- **Cohort 4:** 4 weeks to < 2 years old (n ≥12), which will consist of the following age groups –
  - — **Cohort 4a:** 6 months to < 2 years old (n ≥ 8)
  - — **Cohort 4b**:** 4 weeks to < 6 months old (n ≥ 4)

*Cohort 1 subjects are aged 12 to < 18 years old. No subjects will be enrolled in this age group for Part A as EVG PK data are already available.

**Based on the uncertainty for a dose-exposure relationship in subjects < 2 months old, EVG administration will be restricted to

coadministration with lopinavir/r, and subjects will be enrolled individually and dosed sequentially within the cohort following PK analysis and confirmation of the selected dose of the previous subject(s).

Part A will be enrolled sequentially by age cohort. Enrollment will be limited to Cohort 2 in Part A until EVG safety and PK through Day 10 have been analyzed and determined to be acceptable in subjects aged 6 to < 12 years old. Upon review of safety and PK data in Cohort 2, enrollment will then be limited to Cohort 3 until EVG safety and PK through Day 10 have been analyzed and determined to be acceptable in subjects aged 2 to < 6 years old. Upon review of safety and PK data in Cohort 3, enrollment will then be limited to Cohort 4a until EVG PK through Day 10 and safety through Week 12 have been analyzed and determined to be acceptable in subjects aged 6 months to < 2 years old. Subsequently, Part A enrollment will open for Cohort 4b.

Subjects will participate in an intensive PK evaluation on Day 10. For Cohorts 2 and 3, samples will be collected at 0 (predose, ≤ 30 minutes), 1.5, 2.5, 3.5, 5, 8, 10, and 12 hours postdose. For Cohort 4, samples will be collected at 0 (predose, ≤ 30 minutes), 3, 3.5, 5, and 8 hours postdose.

EVG therapeutic dose confirmation will be established if the 90% confidence interval (CI) of the geometric mean ratio of EVG AUC between the pediatric versus historical EVG exposures are within the bounds of 70-143%. If a subject has EVG C_{tau} levels <44.5 ng/mL and has documented compliance to study drug, the subject will be discontinued.

Subjects with HIV-1 RNA <50 copies/mL at screening are considered to have suppressed viremia and will **only participate in Part A of the study**. These subjects will discontinue EVG and will complete the study following the Day 10 intensive PK visit.

Subjects with HIV-1 RNA >1,000 copies/mL at screening are considered to be failing their antiretroviral regimen and will continue to receive EVG following completion of the Day 10 intensive PK visit for scheduled study visits through Week 48. Data from these subjects will be combined with data from Part B of the study.

Part B

Up to 50 subjects who are failing a current antiretroviral regimen (HIV-1 RNA >1,000 copies/mL) will be enrolled in Part B to evaluate the safety, tolerability and antiviral activity of EVG. The number of additional subjects to be enrolled in Part B will depend

on the number of subjects with HIV-1 RNA >1,000 copies/mL enrolled in Part A who continue EVG therapy beyond Day 10. Overall, a total of 50 subjects in Part A and B combined are planned to complete 48 weeks of EVG therapy.

EVG will be administered for 48 weeks concomitantly with a newly constructed BR selected by the investigator that is based on the subject's antiretroviral history and screening viral resistance results. The BR must include at least 2 fully-active agents, including one of the following fully active PI/r: lopinavir/r (Kaletra), atazanavir/r, darunavir/r, tipranavir/r, or fosamprenavir/r. For subjects < 2 months old, only lopinavir/r is allowed. The BR may contain additional antiretrovirals except for the following: saquinavir, indinavir, nelfinavir, double PI regimens, efavirenz, nevirapine, delavirdine or an integrase strand transfer inhibitor. All PI should be administered according to local product label.

All subjects will take their ritonavir dose based on the dosing schedule prescribed for the PI; no additional ritonavir is required to be taken with EVG.

For Cohort 1 (12 to < 18 year olds), screening in Part B will initiate in parallel with screening in Part A. For Cohorts 2, 3 and 4 in Part B, additional subjects will be screened and initiated sequentially by each age cohort following confirmation of appropriate EVG exposure from the corresponding age cohort in Part A.

Subjects will be enrolled sequentially by cohort as follows:

- **Cohort 1:** 12 to < 18 years old ($n \geq 8$)
- **Cohort 2:** 6 to < 12 years old ($n \geq 8$)
- **Cohort 3:** 2 to < 6 years old ($n \geq 8$)
- **Cohort 4***:** 4 weeks to < 2 years old ($n \geq 4$)

*******Subjects younger than 6 months will not be allowed to enroll in Part B until Part A Cohort 4b data are available indicating acceptable EVG safety and PK through Day 10 in this age group.

Number of Subjects Planned:

Up to 86 subjects

Part A: Approximately 36 evaluable subjects

Part B: Between 14 and 50 subjects, **depending** on the number of subjects with HIV-1 RNA >1,000 copies/mL at screening enrolled in Part A who continue EVG therapy beyond Day 10.

Target Population:	**Part A:** Antiretroviral treatment-experienced, HIV-1 infected male and female subjects, ages 4 weeks to < 12 years, either with suppressed viremia (HIV-1 RNA <50 copies/mL) or failing a current antiretroviral regimen (with HIV-1 RNA >1,000 copies/mL) **Part B:** Antiretroviral treatment-experienced, HIV-1 infected male and female subjects, ages 4 weeks to < 18 years failing a current antiretroviral regimen (with HIV-1 RNA >1,000 copies/mL)
Duration of Treatment:	10 days for subjects with suppressed viremia 48 weeks for subjects failing a current antiretroviral regimen After Week 48, all subjects receiving EVG will be given the option to participate in an extension phase of the study where Gilead will provide EVG until: a) the subject turns 18 and EVG is available for use in adults in the country in which the subject is enrolled or b) the age appropriate EVG formulation becomes available for use in the country in which the subject is enrolled or c) Gilead Sciences elects to terminate development of EVG in the applicable country.

Diagnosis and Main Eligibility Criteria:	**Inclusion Criteria:**
	
	• Antiretroviral treatment-experienced, HIV-1 infected male and female subjects 4 weeks (gestational age of at least 44 weeks) to < 18 years of age
	• Body weight at screening as follows:
	  o Cohort 2 – greater than 15 kg
	  o Cohort 3 – greater than 10.6 kg
	  o Cohort 4 – greater than 5 kg
	• **Part A:** Evidence of suppressed viremia or failing a current antiretroviral regimen as defined below.
	• **Part B:** Evidence of failing a current antiretroviral regimen as defined below.
	
	<u>Criteria for subjects with evidence of suppressed viremia **(Part A only)**</u>:
	
	• Plasma HIV-1 RNA concentration (at least 2 consecutive measurements) at an undetectable level according to the assay being used for at least 3 months prior to screening, and HIV-1 RNA <50 copies/mL (Roche COBAS TaqMan v2.0) at screening.

- Stable antiretroviral regimen including one of the following PI/r for at least 3 months prior to screening: lopinavir/r (Kaletra), atazanavir/r, darunavir/r, tipranavir/r, or fosamprenavir/r. Subjects undergoing dose modifications to their antiretroviral regimen for growth or switching medication formulations are considered to be on a stable antiretroviral regimen.

Criteria for subjects failing a current antiretroviral regimen **(Parts A and B)**:

- HIV-1 RNA >1,000 copies/mL at screening (Roche COBAS TaqMan v2.0)
- Prior treatment for HIV-1 infection, defined as 6 months of antiretroviral treatment experience (with the exception of Cohort 4 where less than 6 months of treatment experience is acceptable) and at least 1 documented resistance mutation as defined by current IAS-USA Guidelines. These resistance mutations must be documented in a historical genotype report(s), or in the genotype report at screening provided by Gilead Sciences.
- Stable antiretroviral regimen (or no antiretroviral regimen) for at least 30 days prior to screening. Subjects undergoing dose modifications to their antiretroviral regimen for growth or switching medication formulations are considered to be on a stable antiretroviral regimen.
- Screening genotype must show full sensitivity to EVG.
- Ability to construct a BR that must contain one of the following fully active PI/r: lopinavir/r (Kaletra), atazanavir/r, darunavir/r, tipranavir/r, or fosamprenavir/r. (Fully active is defined by genotypic analysis.)
- Genotypic sensitivity score (GSS) of at least 2 (including the fully active PI/r and EVG).
- Adequate renal, hematologic, and hepatic function.
- No opportunistic infection within 30 days of study entry

Exclusion Criteria:

- Subjects with the following CD4+ cell counts:
  - For Cohorts 1 and 2: Screening CD4+ cell count < 50 cells/mm^3
  - For Cohort 3: Screening CD4+ cell count < 75 cells/mm^3
  - For Cohort 4: Screening CD4+ cell count < 200 cells/mm^3

- Evidence of active pulmonary or extra-pulmonary tuberculosis disease:
  - — Within 3 months of the Screening visit for all subjects 6 months of age or older
  - — At any time for subjects younger than 6 months
- An ongoing serious infection requiring systemic antibiotic therapy at the time of screening
- An acquired immunodeficiency syndrome (AIDS)-defining condition with onset within 30 days prior to screening
- Life expectancy of < 1 year
- For subjects with HIV-1 RNA >1,000 copies/mL at screening, prior treatment of any duration with an integrase strand transfer inhibitor

Study Procedures/ Frequency:

All Subjects (Parts A and B):

At the Screening, Baseline/Day 1, and all subsequent in-clinic study visits, laboratory analyses (hematology, chemistry and urinalysis), HIV-1 RNA (Roche COBAS TaqMan v2.0), CD4+ cell count and percentage, vital signs, complete or symptom-directed physical examinations, and estimated GFR using the Schwartz formula will be performed.

At the Screening visit, Hepatitis B virus (HBV) and Hepatitis C virus (HCV) serologies will be analyzed (with the exception of Cohorts 3 and 4, where maternal medical history for HBV and HCV will be obtained in lieu of laboratory testing) and supine ECG will be performed. For subjects failing a current antiretroviral regimen (HIV-1 RNA >1,000 copies/mL at screening), HIV-1 integrase, protease and reverse transcriptase genotype will be performed at Screening using the GenoSure PRIme assay.

Subjects enrolled in Part A will participate in an Intensive PK evaluation of EVG on Day 10 (as described below, “Specific Procedures in Part A”). A telephone visit wll occur on Week 1 (Day 7) for safety follow-up assessments.

Subjects with HIV-1 RNA >1,000 copies/mL at screening are considered to be failing a current antiretroviral regimen and will return for study visits at Weeks 4, 8, 12, 16, and then every 8 weeks through Week 48. A telephone visit wll occur on Week 1 (Day 7) and Week 3 for safety follow-up assessments.

Metabolic assessments (glucose and lipid panel [total cholesterol, HDL, direct LDL, and triglycerides]) will be assessed at Baseline,

Week 24, and Week 48 for subjects failing a current antiretroviral regimen (HIV-1 RNA >1,000 copies/mL) and weighing at ≥ 13 kg at the time of the visit.

Tanner Stage assessments (Appendix 6) will be performed for subjects ≥ 6 years of age at the time of the visit, at Baseline, Weeks 24 and 48 or until subjects reach Tanner Stage 5, at which point assessments will no longer be performed. Date of first menses will be documented. For subjects with HIV-1 RNA <50 copies/mL at screening, Tanner Stage assessments will only be completed at the Baseline visit.

Palatability of EVG suspension formulation will be assessed at Baseline, Day 10 (**Part A only**), Week 24, and Week 48, as applicable.

At Weeks 16 and 40, a trough PK sample (20 to 24 hours postdose) will be collected. A random single plasma PK sample will be collected at all Weeks 4, 8, 12 (except for Cohort 3), and 32, for descriptive PK.

Resistance testing will be performed in subjects who experience suboptimal response, virologic rebound, and in subjects at Week 48 or Early Study Drug Discontinuation (ESDD) visit if HIV-1 RNA is ≥ 400 copies/mL.

Adverse events (AEs) and concomitant medications will be assessed at each visit. Treatment adherence will be assessed at all post Baseline visits.

Subjects who are permanently discontinued from the study before Week 48 will be required to complete an ESDD visit within 72 hours of stopping study drug and return to the clinic 30 days after the ESDD visit for a 30-Day Follow-Up Visit.

After Week 48, all subjects receiving EVG will be given the option to participate in an extension phase of the study where Gilead will provide EVG until: a) the subject turns 18 and EVG is available for use in adults in the country in which the subject is enrolled or b) the age appropriate EVG formulation becomes available for use in the country in which the subject is enrolled or c) Gilead Sciences elects to terminate development of EVG in the applicable country. Subjects who are eligible to participate in the study extension must demonstrate evidence of response to EVG or show absence of resistance to EVG for subjects with HIV-1 RNA > 400 copies/mL at Week 48.

	Specific Procedures in Part A Subjects enrolled in Part A will participate in an Intensive PK evaluation of EVG on Day 10. For Cohorts 2 and 3, samples will be collected at 0 (predose, ≤ 30 minutes), 1.5, 2.5, 3.5, 5, 8, 10, and 12 hours postdose. For Cohort 4, samples will be collected at 0 (predose, ≤ 30 minutes), 3, 3.5, 5, and 8 hours postdose. Subject diary cards will be provided to all Part A subjects to record study drugs administration on Days 6-9 prior to the Day 10 Intensive PK visit. • Subjects with HIV-1 RNA <50 copies/mL at screening are considered to have suppressed viremia and will only participate in Part A of the study. These subjects will discontinue EVG after the Day 10 dose and will return to the clinic 30 days after stopping study drug for a 30-Day Follow-Up Visit. • Subjects with HIV-1 RNA >1,000 copies/mL at screening will continue to receive EVG following completion of the Day 10 intensive PK visit and return for subsequent study visits as described above for all subjects. • Subjects who are permanently discontinued from the study before Day 10 will be required to complete an ESDD visit within 72 hours of stopping study drug.
Test Product, Dose, and Mode of Administration:	EVG 50 mg, 85 mg, and 150 mg tablets or EVG powder for oral suspension formulation (5 mg/mL) will be administered orally with food in combination with a BR that must include a PI/r (allowed and disallowed agents are described above in "Study Design"). For subjects weighing ≥ 17 kg and receiving darunavir/r, tipranavir/r or fosamprenavir/r, the EVG dose will be as follows: • 85 mg for subjects ≥ 17 kg to < 28 kg • 100 mg (2 x 50 mg tablets) for subjects ≥ 28 kg to < 34 kg • 150 mg for subjects ≥ 34 kg For subjects weighing ≥ 17 kg and receiving atazanavir/r or lopinavir/r, the EVG dose will be as follows: • 50 mg for subjects ≥ 17 kg to < 30 kg • 85 mg for subjects ≥ 30 kg **Note:** For subjects who are not able to swallow tablets, EVG powder for oral suspension formulation (5 mg/mL) may be administered to obtain EVG doses of 50 mg, 85 mg, 100 mg, or 150 mg.

	For subjects weighing < 17 kg and receiving darunavir/r, tipranavir/r or fosamprenavir/r, the EVG dose will be 4 mg/kg, and for subjects weighing < 17 kg and receiving lopinavir/r or atazanavir/r, the EVG dose will be 2.4 mg/kg, using the EVG powder for oral suspension formulation (5 mg/mL) administered as an oral suspension.
Reference Therapy, Dose, and Mode of Administration:	None.
Criteria for Evaluation:	
Safety:	Adverse events, clinical laboratory tests, and Tanner Stage assessments to evaluate the safety and tolerability of the treatment regimen.
Efficacy:	The percentage of subjects with HIV-1 RNA <50 copies/mL at Weeks 24 (main efficacy endpoint) and 48.
Pharmacokinetics:	The following plasma PK parameters will be estimated: C_{max}, T_{max}, C_{last}, T_{last}, C_{tau}, λ_z, AUC_{tau}, AUC_{last}, CL/F, Vz/F and $T_{1/2}$. The effect of age, EVG dose, and PI/r BR on the PK of EVG will be explored.
Statistical Methods:	For analysis purposes, subjects aged 6 months to < 2 years old (Cohort 4a) and subjects aged 4 weeks to < 6 months old (Cohort 4b) will be combined into one age group (Cohort 4) in Part A. Plasma concentration and parameter of EVG will be summarized using descriptive statistics by age group and overall. EVG exposure PK parameters (AUC_{tau}, C_{tau}, and C_{max}) achieved in pediatric subjects will be compared to historical data. An analysis of variance (ANOVA) using a mixed-effects model appropriate for parallel group design will be fitted to natural-logarithm transformed $AUC_{tau,}$ C_{tau}, and C_{max} of EVG to evaluate whether the exposures of EVG achieved in pediatric subjects are similar to the exposure observed in historical control subjects. EVG exposures (AUC_{tau}, C_{tau}, and C_{max}) generated from population PK modeling will be used as historical control data. Two one-sided tests with each performed at an alpha level of 0.05 and a boundary of 70% to 143% will be used for exposure equivalence assessment.

The percentage of subjects who achieve HIV-1 RNA <50 copies/mL and <400 copies/mL at Weeks 24 and 48 as defined by the FDA snapshot analysis algorithm will be summarized by age group and overall. The 95% confidence intervals will also be presented. The relationship between EVG exposures (AUC_{tau}, C_{tau}, and C_{max}) and virologic failure defined by the snapshot analysis will be explored.

The change from baseline in log_{10} HIV-1 RNA, CD4+ cell count, and CD4 percentage will be summarized by visit, age group, and overall using descriptive statistics.

The incidences of treatment-emergent adverse events and treatment-emergent laboratory abnormalities will be summarized by age group and overall.

Palatability of oral suspension formulation of EVG will be summarized using descriptive statistics by appropriate age group and overall.

For each age group and overall, Tanner Stages at Weeks 24 and 48 will be summarized by baseline Tanner Stage using frequency and percentage. Age of first menses will be summarized descriptively.

A total of 12 pediatric subjects each in Cohorts 2 – 4 compared to 334 HIV-infected historical control subjects included in the EVG population PK modeling will provide at least 90% power to conclude exposure equivalence of EVG AUC_{tau} and C_{max} in pediatric subjects vs. in historical control subjects, assuming the expected geometric mean ratio is 1, equivalency boundary is 70% to 143%, 2 one-sided tests are each performed at an alpha level of 0.05, and the standard deviation is 0.36 ng•hr/mL for AUC_{tau} and 0.28 ng/mL for C_{max} (natural log scale, estimated from EVG population PK modeling).

A total of 12 subjects each in Cohorts 2-4 will also provide at least 80% power to target a 95% confidence interval within 60% and 140% of the geometric mean estimate of clearance and volume of distribution of EVG respectively, assuming a coefficient of variation (CV) of 42.3% for clearance and 22.9% for volume of distribution (estimated from EVG population PK modeling).

A total of 50 subjects from Parts A and B combined will provide for reasonable assessment of safety through Week 48 in subjects < 18 years of age. For the main secondary efficacy endpoint, assuming a virologic success rate of 60% (based on Study GS-US-183-0145 in adults) in this population of antiretroviral treatment-experienced subjects receiving a new class drug,

i.e., EVG, a sample size of 50 subjects will result in a 95% confidence interval (CI) for the response rate from 46% to 74% (i.e., an error margin of 14%).

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

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

° C	degrees Celsius
° F	degrees Fahrenheit
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANC	absolute neutrophil counts
ARV	Antiretroviral
ANOVA	analysis of variance
AST	Aspartate aminotransferase
ATV	Atazanavir
ATV/co	cobisistat-boosted atazanavir
ATV/r	ritonavir-boosted atazanavir
AUC	area under the plasma/serum/peripheral blood mononuclear cell concentration versus time curve
AUC_{tau}	the area under the concentration verses time curve over the dosing interval
AV	Atrioventricular
BR	background regimen
BMD	bone mineral density
BUN	blood urea nitrogen
CBC	complete blood count
CI	confidence interval
CL_{cr}	creatinine clearance
C_{max}	the maximum observed serum/plasma/peripheral blood mononuclear (PBMC) concentration of drug
C_{last}	the last observed quantifiable concentration of the drug in plasma
COBI	cobicistat (GS-9350)
CNS	central nervous system
C_{tau}	the observed drug concentration at the end of the dosing interval
CPI	comparator protease inhibitor
CPK	creatine phosphokinase
CRO	contract (or clinical) research organization
CV	Coefficient of Variation
CYP	cytochrome P450
DAVG	average area under the dosing interval
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DRV	darunavir
DSPH	Drug Safety and Public Health
EC	Ethics Committee

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

ECG	Electrocardiogram
eCRF	electronic case report form(s)
EVG	elvitegravir (GS-9137)
EVG/co	cobicistat-boosted elvitegravir
EVG/COBI/FTC/TDF	Single tablet regimen of elvitegravir (EVG) 150 mg/ cobicistat (COBI) 150 mg emtricitabine (FTC) 200 mg/tenofovir disoproxil fumarate (TDF) 300 mg
EVG/r	ritonavir-boosted elvitegravir
Emax	model predicted maximum efficacy
FDA	(United States) Food and Drug Administration
FTC	emtricitabine, Emtriva®
FTC/TDF	emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg, Truvada®
GCP	Good Clinical Practice (Guidelines)
GFR	glomerular filtration rate
GGT	gamma glutamyl transferase
GLP	Good Laboratory Practices
GSI	Gilead Sciences, Inc.
GSS	Genotypic sensitivity score
GS-9137	elvitegravir, 6-(3-Chloro-2-fluorobenzyl)-1-[(2S)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1, 4-dihydroquinoline-3-carboxylic acid
GS-9350	cobicistat, 1,3-Thiazol-5-ylmethyl (2R,5R)-(5-(((2S)-2-((methyl((2-(propan-2-yl)-1,3-thiazol-4-yl(methyl(carbamoyl)amino((-4-(morpholin-4-yl)butanamido(-1,6-diphenylhexan-2-yl)carbamate
HAART	highly active antiretroviral therapy
HBV	hepatitis B virus
HCV	hepatitis C virus
HDPE	high-density polyethylene
hERG	human Ether-à-go-go Related Gene
HIV	Human Immunodeficiency Virus
HMG-CoA	5-hydroxy-3-methylglutaryl-coenzyme A
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ID	Identification
IND	Investigational New Drug (Application)
INSTI	integrase strand transfer inhibitor
IRB	Institutional Review Board
IV	Intravenous
KS	kaposi's sarcoma
LC/MS/MS	liquid chromatography – tandem mass spectrometry

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

LLN	lower limit of the normal range
LPV	lopinavir
MDRD	modification of diet in renal disease
MDZ	Midazolam
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
mmHg	millimeters mercury
mtDNA	mitochondrial DNA
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
NSAID	non-steroidal anti-inflammatory drug
OBT	optimized background therapy
PI	protease inhibitor
PI/r	ritonovir boosted-protease inhibitor
PK	Pharmacokinetic
PR	pulse rate
PPI	proton pump inhibitor
PT	preferred term (in Section 7)
PT	prothrombin time (in Appendix 5)
QD	once daily
QTc	corrected QT
RAL	Raltegravir
RNA	ribonucleic acid
RTV	ritonavir, Norvir®
SAE	serious adverse event
Scr	serum creatinine
STR	Single Tablet Regimen
SUSAR	Suspected Unexpected Serious Adverse Reaction
T½	half life
TDF	tenofovir disoproxil fumarate, Viread®
TFV	Tenofovir
TLOVR	time to loss of virologic response
t_{max}	the time (observed time point) of Cmax
TPR	tipranavir
TPV/r	ritonavir-boosted tipranavir
Ucr	urine creatinine
UGT	uridine glucuronosyltransferase
ULN	upper limit of the normal range

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS (CONTINUED)

US	United States
λz	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the plasma concentration of drug verses time curve

1. INTRODUCTION

1.1. Background

HIV-1 infection is a life-threatening and serious disease that is of major public health interest around the world. Globally, it was estimated that approximately 33 million people were living with HIV-1 in 2009, including 2.5 million children under 15 years of age {16695}. In the European Union (EU), 26,220 newly diagnosed cases of HIV-1 infection were reported in 2006, a rate of 67.2 per million people {15984}. In the US there were an estimated 42,959 diagnoses of HIV-1 infection reported in 2009 and among these an estimated 2,244 were in children < 19 years of age {17375}, indicating a continuous prevalence of HIV-1 infection in US pediatric and adolescent populations.

The infection, if left untreated or suboptimally treated, is characterized by deterioration in immune function, the subsequent occurrence of opportunistic infections and malignancies, ultimately resulting in death. Therapeutic strategies for the treatment of HIV-1 disease have been significantly advanced by the availability of highly active antiretroviral therapy (HAART); the introduction of HAART was associated with a dramatic decrease in acquired immune deficiency syndrome (AIDS)-related morbidity and mortality {2537}, {5125}, {8284}. While combination antiretroviral therapy has been largely successful in reducing the morbidity and mortality associated with HIV disease, a significant proportion of patients eventually experience loss of virologic, immunologic, or clinical benefit from their current regimens.

Suboptimal adherence and subsequent exposure to multiple antiretroviral regimens over time often leaves chronically-infected patients with limited options for alternative treatment regimens. Developing safe and effective therapies for treatment-experienced patients with documented three- or four-class antiretroviral drug resistance remains a priority. Current treatment guidelines suggest several approaches to the management of treatment-experienced HIV-infected patients {11575}. The evaluation of patients with treatment failure includes assessment of virologic, immunologic and clinical status; determination of the cause of treatment failure; and review of pharmacokinetic parameters. In addition, resistance testing while patients are still taking their failing regimen provides additional information to identify active antiretroviral drugs for inclusion in their subsequent treatment regimen {9302}.

Incomplete adherence to ARV regimens is a critical factor contributing to the development of viral resistance and treatment failure and thus is a primary barrier to successful long-term treatment. Total pill burden, dosing frequency, and safety concerns are among the greatest obstacles to achieving adherence {4266}, {4256}. This is supported by studies in which simple, once-daily HAART regimens demonstrate high levels of adherence and treatment satisfaction {7034}, {7035}, {7036}. The potential for noncompliance in pediatric patients is well known and is recognized in ICH E11. HIV treatment guidelines recommend that unless a clinically inappropriate reason is identified, patients ought to be prescribed once-daily HAART. Thus, there remains a need for developing additional, simplified once-daily single

tablet regimens that combine potent and sustained efficacy, favorable tolerability, minimal long-term toxicity, and practical, convenient dosing.

Treatment-experienced HIV-infected children failing currently available regimens have limited well-tolerated, once-daily treatment options. For these patients, newer treatments targeting alternative steps in the viral replication cycle are needed to preserve their immune function and prevent clinical progression. In all patients, the ideal goal of therapy remains complete suppression of HIV ribonucleic acid (RNA).

1.2. Elvitegravir (EVG, GS-9137)

Detailed information is available in the current version of the elvitegravir Investigator's Brochure (IB).

1.2.1. General Information

HIV belongs to the *Lentivirus* genus of the *Retroviridae* family that has two copies of an approximately 9.5 kb single-stranded RNA genome. Following viral entry and reverse transcription of the viral genome, the resulting linear viral deoxyribonucleic acid (DNA) migrates into the nucleus and is integrated into the host cell genomic DNA forming a provirus. This integration reaction is catalyzed by the viral-encoded enzyme integrase. This enzyme is thus an attractive target for selective anti-HIV therapy since there is no known functional homologue in human cells.

Elvitegravir (chemical name: 6-(3-Chloro-2-fluorobenzyl)-1-[(2*S*)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1, 4-dihydroquinoline-3-carboxylic acid) is a low molecular weight HIV-1 integrase inhibitor that specifically inhibits integration of viral DNA into the host chromosomal DNA in cell culture. Elvitegravir does not inhibit HIV-1 reverse transcriptase or protease enzymes, or human topoisomerase I and II. Elvitegravir showed potent anti-HIV activity against both laboratory strains and clinical isolates with EC_{50} values ranging from 0.02 to 1.7 nM. The EC_{50} value of elvitegravir in the presence of 50% human serum is 1.5 nM using HIV-1 IIIb-infected human peripheral blood mononuclear cell cultures. Elvitegravir also exhibited potent antiviral activity against virus with resistance to NRTIs, NNRTIs and PIs.

1.2.2. Preclinical Pharmacology and Toxicology

Single and multiple oral dose toxicity studies (13-week mouse; 1-, 3-, and 6-month rat; 1- and 9-month dog), a 1-month repeated oral dose immunotoxicity study in rats, reproductive toxicity (including a 28-day juvenile toxicity evaluation in rats), genotoxicity and safety pharmacology studies have been performed with elvitegravir and revealed no significant toxicities. In long-term carcinogenicity studies with elvitegravir, no drug-related increases in tumor incidence were found in mice at doses up to 2000 mg/kg/day (approximately 3 or 5 times the human systemic exposure at the therapeutic dose of 150 mg/day) or in rats at doses up to 2000 mg/kg/day (approximately 16 to 35 times human systemic exposure at the 150 mg/day therapeutic dose). In a mouse study, high-dose

elvitegravir (2000 mg/kg/day) was also administered in combination with ritonavir as ritonavir substantially increased elvitegravir exposure in mice. No drug-related increases in tumor incidence were noted in these animals at exposures approximately 18 times the systemic exposure in humans at the maximum therapeutic elvitegravir dose.

Two bridging toxicity studies conducted with elvitegravir in combination with ritonavir, a 90-day toxicity study and an embryo-fetal development study in rats, revealed no additional toxicities. No effects were seen in studies to investigate potential for inducing quinolone-specific toxicity performed because elvitegravir has a quinolone moiety in its molecular structure. These included a single oral dose phototoxicity study in mice and a single oral dose study of possible synergistic effects (specifically, drug-induced convulsions) of elvitegravir and an NSAID (fenbufen) in mice. In the studies of the cardiovascular and respiratory systems in conscious Beagle dogs at doses up to 100 mg/kg, elvitegravir did not produce adverse effects on blood pressure, heart rate, the electrocardiogram (ECG), respiratory rate, or oxygen saturation. Elvitegravir at concentrations of 0.1 and 1 μM had no effect on the hERG tail current in vitro.

There were no significant adverse effects observed in studies where elvitegravir was administered in combination with ritonavir. Additionally, no significant adverse events were observed in the safety, pharmacology, mutagenicity, reproductive, and immunotoxicity studies or special studies to investigate potential quinolone-related toxicity.

Exposures in the chronic 9-month dog toxicity study were 2- to 3-fold above the estimated human exposure at a dose of elvitegravir 150 mg + ritonavir 100 mg; similar or greater safety margins were observed in repeat-dose rodent studies.

Elvitegravir undergoes metabolism primarily by cytochrome (CYP) P450-mediated oxidation and glucuronic acid conjugation (glucuronidation). Following elvitegravir/r dosing, elvitegravir is the predominant circulating species in plasma (~ 94%), with low levels of metabolites from hydroxylation and/or glucuronidation pathways, including GS-9200 (M4; acyl glucuronide metabolite) produced by UDP-glucuronosyltransferase (UGT) 1A1/3 and GS-9202 (M1; primary hydroxylated metabolite) produced by CYP3A4, and whose formation is inhibited by ritonavir. Mean plasma exposures of the M1 metabolite were below the limit of quantitation in all clinical studies. M4 plasma levels relative to parent (i.e., mean M4:parent ratio) were less than 10% in all phase 1 studies and 15% to 24% in a Phase 2 study. M4 exposures were 4- to 6-fold lower in humans compared to those observed during nonclinical toxicology studies. Additionally, the M1 and M4 metabolites are markedly less potent (M1: 5- to 18-fold and M4: 10- to 38-fold in antiviral activity assays) than the parent drug, thus metabolites are not considered to contribute to the antiviral activity of elvitegravir. Urinary elimination of elvitegravir is a minor pathway with ~ 6.7% of a dose excreted in urine. In vitro, incubation of elvitegravir in human microsomes in the presence of ketoconazole (a CYP3A4 inhibitor) was able to almost completely inhibit formation of the primary oxidative metabolite M1 (70% and 98% at concentrations of 0.2 and 2.0 μM, respectively). In vitro data also suggest that elvitegravir may induce its own metabolism as well as potentially that of other CYP3A4 substrates (both the impact of CYP3A4 inhibition

and potential for induction of its metabolism, when dosed alone, have been confirmed in clinical studies).

Elvitegravir was tested in a standard in vitro assay for specific effects on the synthesis of mitochondrial DNA (mtDNA) in HepG2 liver cells. Following 14 days of treatment, elvitegravir did not show any specific effect on the content of mtDNA, a result consistent with the lack of inhibition of DNA polymerase gamma.

1.2.3. Clinical Trials of Elvitegravir

As of 16 November 2012, a total of 327 HIV-1 infected subjects and 963 HIV uninfected subjects had been dosed with EVG as a single agent in Phase 1 and 2 clinical studies. In addition, 354 HIV-1 infected, ARV treatment-experienced subjects have received EVG in an ongoing Phase 3 study.

1.2.3.1. Clinical Pharmacokinetics

Elvitegravir exhibits less than dose-proportional pharmacokinetics over the dose range of 20 to 300 mg, likely due to decreased absorption likely due to solubility-limited dissolution.

Coadministration of elvitegravir with low-dose ritonavir (RTV, 100 mg; elvitegravir/r) to healthy adults substantially increases the relative oral bioavailability and slows the apparent clearance of elvitegravir, resulting in approximately 20-fold improvement in systemic exposure (AUC) and high trough (C_{tau}) concentrations thereby allowing for once-daily dosing. A ritonavir dose of 100 mg is sufficient to boost oral elvitegravir; higher doses of ritonavir do not result in additional increases in elvitegravir systemic exposure. Once-daily elvitegravir administration at a dose of 50 mg + RTV provides C_{tau} values greater than the in vitro protein-adjusted IC_{95} {9320}.

1.2.3.1.1. Pharmacokinetic (Drug-Drug) Interactions

A number of healthy adult volunteer studies have been conducted investigating drug-drug interaction between elvitegravir and HIV nucleoside/nucleotide analogue reverse transcriptase inhibitors (NRTIs), the non-nucleoside reverse transcriptase inhibitor (NNRTI) etravirine, the human chemokine receptor CCR5 antagonist maraviroc and protease inhibitors (PIs). Results from studies with NRTIs including emtricitabine/tenofovir disoproxil fumarate (TRUVADA®), zidovudine, didanosine, stavudine and abacavir indicate no clinically relevant drug-drug interactions necessitating dose modifications of these agents or elvitegravir/r upon their coadministration. These findings are consistent with the differing elimination pathways for the NRTIs (predominantly renal and extra-hepatic metabolism, if any) versus elvitegravir and ritonavir (cytochrome P450 and Phase 2 metabolism). Further, no clinically relevant drug-drug interaction was observed between elvitegravir/r and etravirine, allowing coadministration of these agents without dose modification. Coadministration of elvitegravir/r, a net CYP3A inhibitor, with maraviroc resulted in no clinically relevant change in elvitegravir pharmacokinetics; however, maraviroc exposure was 2- to 4-fold higher in the presence of elvitegravir/r. When coadministered with CYP3A4

inhibitors (including ritonavir-boosted protease inhibitors [except tipranavir/r]), an adjustment of maraviroc dose is recommended.

Clinical drug-drug interaction studies designed to evaluate the pharmacokinetics of elvitegravir when used within the context of ritonavir-boosted PI antiretroviral regimens in healthy adults have also been conducted. In these studies elvitegravir + 100 mg RTV was compared to elvitegravir in combination with a ritonavir-boosted protease inhibitor, where the ritonavir dose/dosing frequency used was the dose/dosing frequency indicated for use with the PI under study (elvitegravir + PI/r).

Results from these studies have shown that coadministration of elvitegravir plus ritonavir-boosted tipranavir (TPV/r; 500/200 mg BID), darunavir (DRV/r; 600/100 mg BID), or fosamprenavir (FPV/r 700/100 mg BID) did not result in a pharmacokinetic drug interaction. Therefore, elvitegravir can be coadministered (added) to TPV/r-, DRV/r-, or FPV/r-containing regimens without dose modification. Data from studies examining coadministration with lopinavir/r (LPV/r; 400/100 mg BID) or atazanavir/r (ATV/r; 300/100 mg QD) indicate substantially higher elvitegravir systemic exposures (AUC: increased 75% and 100%, respectively) and trough concentrations (C_{tau}: increased 136% and 188%, respectively) by these two protease inhibitors. A dose reduction of elvitegravir is being used in this study when it is administered with these two boosted PIs to achieve similar AUC and maintenance of high trough concentrations. In a multiple dose clinical study in healthy adults (GS-US-183-0106), equivalent elvitegravir exposures (C_{max} and AUC) were observed with 85 mg plus atazanavir/r versus elvitegravir/ritonavir 150/100 mg. Concomitant administration of elvitegravir with LPV/r and ATV/r do not significantly affect the pharmacokinetics of lopinavir or atazanavir, and no dose modification of these PIs is required.

Elvitegravir/r simultaneously coadministered with antacids can lead to lower elvitegravir levels, putatively via complexation with divalent cations present at high concentrations in antacids. Separation of elvitegravir/r dosing from antacid by at least 2 hours minimizes the impact on elvitegravir absorption. Coadministration with a representative proton pump inhibitor (PPI, omeprazole) had no effect on elvitegravir/r exposures, indicating that the interaction of elvitegravir with antacids is due to a local effect on drug absorption and not a more general effect of gastric pH.

Coadministration of EVG/r and dose-reduced rifabutin (150 mg every other day) resulted in equivalent exposures of EVG and rifabutin, relative to those observed with EVG/r or rifabutin (300 mg once daily) administered alone (GS-US-183-0125) {12104}. Plasma exposure of the active metabolite of rifabutin, 25-O-desacetylrifabutin, which is equipotent with the parent on a molar basis, was increased 5- to 20-fold by EVG/r. The total antimycobacterial activity of rifabutin was increased by 50% during coadministration with EVG/r. These results are consistent with data from drug interaction studies with other RTV-boosted agents. Dose reduction of rifabutin to 150 mg every other day or 3 times weekly is recommended during coadministration with EVG/r. Patients receiving EVG/r and rifabutin should be closely monitored for AEs associated with rifabutin.

Coadministration of ketoconazole (200 mg twice daily) with EVG/r resulted in modest increases in both EVG (< 50%) and ketoconazole exposure (as compared with historical data) (Study GS-US-183-0146). Overall, the magnitude of the interaction between EVG/r and ketoconazole does not necessitate EVG dose reduction in the setting of ketoconazole. However, because of the changes in ketoconazole pharmacokinetics, and consistent with dosing recommendations with other RTV-boosted agents, a maximum daily ketoconazole dose of 200 mg is recommended in the setting of EVG/r.

Methadone (80 to 120 mg once daily) pharmacokinetics were unaffected by coadministration of EVG 150 mg boosted with cobicistat 150 mg once daily (EVG/co). When EVG/co (150/150 mg once daily) was coadministered with buprenorphine/naloxone (16/4 to 24/6 mg once daily), buprenorphine and norbuprenorphine exposures were modestly higher (35.3% and 42.4%, respectively), and naloxone exposure was modestly lower (28.4%) than when buprenorphine/naloxone was dosed alone. These changes were not considered clinically relevant. No meaningful changes in opioid pharmacodynamics as assessed by subjective and objective opiate withdrawal and overdose assessment scales were noted when EVG/co was coadministered with methadone or buprenorphine/naloxone (Study GS-US-216-0125). Accordingly, no dose adjustments of methadone or buprenorphine/naloxone are required when coadministered with EVG/co. In each case, EVG and COBI exposures were consistent with historical data obtained following their administration as EVG/co alone, or as components of the EVG/COBI/FTC/TDF STR (Stribild™).

In these Phase 1 clinical studies in adults, mild headache, nausea, and diarrhea were the most common side effects. Two serious adverse events were reported: one early-term miscarriage with possible attribution to elvitegravir/r and midazolam due to unclear etiology, and one congenital abnormality considered not related to elvitegravir (bilateral, fifth-finger appendages, most likely skin tags) in an otherwise healthy infant born to a study subject. No deaths were reported in these studies. In these Phase 1 clinical studies, healthy volunteers received elvitegravir/r once daily at doses ranging from 50/100 to 250/100 mg for up to 28 days, and elvitegravir/r appeared to be well tolerated.

1.2.3.2. QT/QT_C Interval Study

Results from Study GS-US-183-0128, a Phase 1, randomized, comparative, positive and placebo-controlled, parallel group study of the effects of elvitegravir/r on the QT/QTc interval in healthy male and female adult subjects, demonstrated that there is no significant effect on the QTc interval in either dosing regimen of elvitegravir/r (125/100 mg or 250/100 mg for 10 days). Both the 125 and 250 mg doses of elvitegravir were well-tolerated in this study. The 125 mg dose provided exposures similar to the 150 mg dose under study in this protocol.

1.2.3.3. Elvitegravir Pediatric Formulation Pharmacokinetic Study

In a Phase 1 study in healthy adult volunteers (Study GS-US-183-0149), the pharmacokinetics of 2 pediatric EVG formulations were compared to the adult EVG

formulation in an open-label, crossover, randomized, multiple cohort, single-center study. The plasma EVG concentrations of 150 mg of either the adult EVG formulation (1 × 150 mg tablet), the EVG pediatric tablets (3 × 50 mg tablets) and the EVG pediatric suspension (30 mL of a 5 mg/mL suspension), each administered as a single dose with 100 mg of ritonavir in the fed state, were compared. Preliminary findings show that RTV-boosted EVG exposures were comparable across treatments. Bioequivalent EVG exposures (AUC_{last}, AUC_{inf}, and C_{max}) were observed following administration of EVG pediatric tablets or EVG pediatric suspension, relative to adult EVG formulation (Table 1-1). All treatments were generally well tolerated.

Table 1-1. GS-US-183-0149: EVG Pharmacokinetic Parameters and Statistical Comparison following EVG pediatric tablets or EVG pediatric suspension versus adult EVG formulation

EVG PK Parameter	Mean (%CV)		Geometric Least-Squares Means Ratio (%) (90% CI)
	Test EVG Pediatric Tablets (N = 30)	Reference Adult EVG Formulation (N = 30)	
AUC_{inf} (ng•h/mL)	22224.9 (34.5)	22148.1 (36.2)	100.07 (93.77,106.78)
AUC_{last} (ng•h/mL)	21130.9 (31.9)	20976.2 (29.1)	99.60 (93.17,106.48)
C_{max} (ng/mL)	1648.3 (29.8)	1639.2 (28.5)	100.02 (93.10,107.45)
EVG PK Parameter	**Mean (%CV)**		**Geometric Least-Squares Means Ratio (%) (90% CI)**
	Test EVG Pediatric Suspension (N = 26)	**Reference Adult EVG Formulation (N = 26)**	
AUC_{inf} (ng•h/mL)	25005.7 (35.8)	22827.9 (36.4)	105.21 (100.00,110.69)
AUC_{last} (ng•h/mL)	24221.9 (36.3)	21813.5 (37.2)	105.15 (99.92,110.65)
C_{max} (ng/mL)	1800.4 (40.1)	1650.6 (37.5)	108.01 (100.91,115.61)

1.2.3.4. Clinical Trials in HIV-1 Infected Adult Subjects

Data from Study GS-US-183-0101 (proof-of-concept), a Phase 1, double-blind, randomized, placebo-controlled study in treatment-naive and treatment-experienced HIV-infected patients, demonstrated that elvitegravir has potent antiretroviral activity (~ 2 $\log_{10}$ copies/mL reduction) at doses of 400 to 800 mg twice daily or 50 mg once daily when boosted with ritonavir 100 mg for 10 days with no clinically significant adverse events or laboratory abnormalities {9320}. An E_{max} dose-response model demonstrated that antiviral activity was strongly associated with elvitegravir steady-state C_{tau} concentrations.

Study GS-US-183-0105 was a randomized, partially-blinded, active-controlled, dose-ranging, 48-week, Phase 2 study. The study was designed to assess the non-inferiority of ritonavir-boosted elvitegravir versus ritonavir-boosted comparator PIs both in combination with an optimized background therapy (OBT) in HIV-1 infected treatment-experienced subjects. At screening, subjects were to have a plasma HIV RNA load ≥ 1000 copies/mL and documented presence of at least one protease gene mutation as defined by the IAS-USA 2006 Guidelines {9302}.

A total of 297 patients were randomized (1:1:1:1) to four treatment arms each of which included OBT with at least two agents not including a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor (randomization was stratified by the use of T-20):

- Arm 1 – Comparator protease inhibitor boosted with ritonavir (CPI/r) + OBT
- Arm 2 – Elvitegravir 20 mg/ritonavir 100 mg + OBT
- Arm 3 – Elvitegravir 50 mg/ritonavir 100 mg + OBT
- Arm 4 – Elvitegravir 125 mg/ritonavir 100 mg + OBT

The primary endpoint was the time-weighted mean change from baseline in HIV-1 RNA at Week 24 ($DAVG_{24}$). The $DAVG_{24}$ of the elvitegravir/r 125 mg treatment arm (−1.7 $\log_{10}$ copies/mL) was superior to that of the CPI/r arm (−1.2 $\log_{10}$ copies/mL; 95% CI −0.8, −0.05; p = 0.0094). At Week 24, the proportions of patients who received elvitegravir/r 125 mg with > 1 $\log_{10}$ reduction in HIV-1 RNA from baseline, HIV-1 RNA < 400 copies/mL or HIV-1 RNA < 50 copies/mL are non-inferior to the proportions of patients achieving the same responses in the CPI/r arm. The magnitude and durability of virologic suppression in subjects who received elvitegravir 125 mg correlated with the activity of background therapy; for example, 74% of subjects given elvitegravir 125 mg with naive use of T-20 achieved HIV RNA < 50 copies/mL by Week 16.

Elvitegravir/r was well-tolerated in this study. The incidences of Grade 3 and 4 adverse events, treatment-emergent adverse events leading to study drug discontinuation, serious adverse events, and Grade 3 and 4 laboratory abnormalities across the elvitegravir/r treatment arms were similar to the incidences in the CPI/r group and were not dose related. Two serious adverse events were reported as related/possibly related to elvitegravir/r, including a hypersensitivity reaction and syncope. Three subjects treated with elvitegravir/r died during the trial. The cause of death was cardiorespiratory failure with underlying cachexia and acquired immune deficiency syndrome, pneumocystis infection, and large B-cell lymphoma. None of the deaths were assessed as related to elvitegravir/r, but likely due to the subjects' underlying HIV infection.

Study GS-US-183-0130 is an ongoing, Phase 2, open-label, multicenter study of the safety of EVG/r administered in combination with a background ARV regimen to HIV-1 infected adult and adolescent subjects who had completed a prior EVG/r treatment study without

experiencing treatment-limiting toxicity, regardless of whether or not they had received EVG in that study, and regardless of their baseline plasma HIV-1 RNA level.

Data are available from an interim analysis at Week 192, conducted when all adult subjects from Study GS-US-183-0105 had completed 192 weeks of treatment. The adolescent subjects who rolled-over from Study GS-US-183-0152 (described below) had completed a median 32 weeks of treatment.

A total of 192 subjects were enrolled in the study, 184 adults (95.8%) from Study GS-US-183-0105 and 8 adolescents (4.2%) from Study GS-US-183-0152. The interpretation of efficacy data in this study is difficult because of the inclusion of subjects who had (n = 162) and had not (n = 30) received EVG in their prior study, subjects with baseline HIV-1 RNA levels < 50 copies/mL and ≥ 50 copies/mL, a high attrition rate during the study for reasons other than lack of efficacy or death (79 of 192 subjects; 41.1%), and the lack of a comparator arm.

Percentages of subjects with a plasma HIV-1 RNA level < 50 copies/mL at different study time points are shown in Table 1-2.

Table 1-2. GS-US-183-0130: Proportions of Subjects with Plasma HIV-1 RNA < 50 Copies/mL at Study Time Points (Efficacy Analysis Set)

	Baseline HIV-1 RNA			
	< 50 Copies/mL (n = 84)		≥ 50 Copies/mL (n = 107)	
Week	M = F[a]	M = E[b]	M = F[a]	M = E[b]
48	86.6%	89.9%	25.7%	36.1%
96	76.8%	86.3%	28.7%	46.0%
144	72.0%	88.1%	29.7%	58.8%
192	68.3%	90.3%	30.7%	70.5%

a Missing = Failure. M = F, in which subjects with missing data for a visit were counted as a failure for that visit, was used for the primary analysis. Subjects who had missing data for a visit because they had not yet reached the end of the analysis window for that visit were excluded from that visit and all subsequent visits.

b Missing = Excluded. M = E analysis, in which subjects with missing data were excluded entirely, was used for secondary analysis.

In subjects with baseline HIV-1 RNA < 50 copies/mL, EVG administered in combination with a background ARV regimen showed durable efficacy.

Long-term virologic suppression was achieved in approximately one-third of subjects with baseline HIV-1 RNA ≥ 50 copies/mL, most of whom had received EVG uninterrupted from their previous study. This low level of efficacy as determined by the missing = failure (M = F) analysis in these subjects can be attributed to the inclusion in the study of subjects who were treatment-experienced and had received EVG in a prior study (GS-US-183-0105 or GS-US-183-0152) and who had virologic failure at the end of that study. Virology data from

the previous studies indicated that many subjects who rolled-over into Study GS-US-183-0130 did not have an effective background regimen and had developed mutations associated with EVG resistance. Additionally, the attrition rate among these subjects was high (58 of 107 subjects; 54.2%), and baseline genotyping was not performed, meaning that background ARV regimens were not optimized.

For subjects with baseline HIV-1 RNA < 50 copies/mL (n = 84), HIV-1 RNA levels (log_{10} copies/mL) were maintained over 192 weeks. For subjects with baseline HIV-1 RNA ≥ 50 copies/mL (n = 107), HIV-1 RNA levels decreased over 192 weeks. The mean value at baseline for these subjects was 3.51 log_{10} copies/mL. Mean changes from baseline in plasma HIV-1 RNA levels at Weeks 48, 96, 144, and 192 were –0.52, –0.44, –0.66, and -0.67 log_{10} copies/mL, respectively. CD4 cell counts increased over time in both baseline plasma HIV-1 RNA level subject groups (< 50 copies/mL and ≥ 50 copies/mL).

Of the 49 subjects who qualified for resistance testing, 37 subjects (76%) entered the study with preexisting INSTI resistance mutations that had developed during their original treatment in Study GS-US-183-0105. Among these subjects, 31 gained additional INSTI resistance mutations during the 192-week analysis period of the current study. Six of the 12 subjects tested who had no evidence of INSTI resistance at study entry developed INSTI resistance mutations in the current study.

Within the overall resistance analysis population, E92Q was the most common INSTI resistance mutation to develop, consistent with observations from GS-US-183-0105. Mutations at position E92 were also the most commonly lost during the current study, reflecting the presence of these mutations at study entry and the subsequent evolution of INSTI resistance to other patterns of INSTI mutations. Only 5 of the 84 subjects (6%) who entered the study with HIV-1 RNA < 50 copies/mL qualified for resistance testing, 3 of whom developed INSTI resistance mutations during the current study.

EVG/r was well tolerated in Study GS-US-183-0130. Treatment-emergent AEs reported for at least 10% of subjects were upper respiratory tract infection, diarrhea, sinusitis, bronchitis, nasopharyngitis, nausea, fatigue, arthralgia, depression, and back pain. Most treatment-emergent AEs reported were mild (Grade 1) or moderate (Grade 2) in severity, and most were considered by the investigator to be not related to study drug. Among those AEs that were considered related to study drug, reported in at least 12.5% of subjects, only pain in extremity, peripheral neuropathy, and alopecia (each reported by 2 subjects) occurred with greater than single subject incidence. Four subjects (2.1%) experienced a Grade 3 or Grade 4 AE considered by the investigator to be related to study drug (acute pancreatitis, hepatitis B, and peripheral neuropathy [2 subjects]), all of which were Grade 3 in severity. There were 11 deaths during the Week 192 analysis period, none of which was considered by the investigator to be related to study drug. No AE leading to study drug discontinuation was reported for more than 1 subject, none was considered by the investigator to be related to study drug, and all but 1 (renal failure) was an SAE.

Among the 192 HIV-1 infected subjects enrolled, 72 subjects (37.5%) experienced a treatment-emergent SAE during the Week 192 analysis period. Treatment-emergent SAEs reported for more than 1 subject included pneumonia (3.1%), cellulitis (2.1%), myocardial infarction (1.6%), chest pain (1.6%), gastroenteritis (1.6%), influenza (1.6%), acute renal failure (1.6%), anemia (1.0%), congestive cardiomyopathy (1.0%), pyrexia (1.0%), esophageal candidiasis (1.0%), *Pneumocystis jiroveci* pneumonia (1.0%), dehydration (1.0%), osteonecrosis (1.0%), depression (1.0%), mental status changes (1.0%), deep vein thrombosis (1.0%), and hypotension (1.0%). None of these treatment-emergent SAEs reported for more than 1 subject was considered by the investigator to be related to study drug. Two subjects had a treatment-emergent SAE that was considered by the investigator to be related to study drug (Grade 3 acute pancreatitis and Grade 2 necrotizing retinitis).

Study GS-US-183-0145 is an ongoing, Phase 3, double-blind, double-dummy, multicenter, randomized, active-controlled study to evaluate the safety and efficacy of EVG/r versus RAL, each administered with a background regimen (BR), in approximately 700 HIV-1 infected, ARV treatment-experienced adults with plasma HIV-1 RNA levels ≥ 1000 copies/mL and documented resistance (as defined by current International Antiviral Society-USA guidelines) or at least 6 months experience prior to screening with 2 or more different classes of ARV agents.

A total of 712 subjects were randomized in a 1:1 ratio, stratified by HIV-1 RNA level (≤ 100,000 copies/mL or > 100,000 copies/mL) at screening, and the second agent class (NRTI/other), to one of the following 2 treatment groups:

- Treatment Group 1: EVG 150 mg once daily + RAL placebo twice daily + BR (n=354). The EVG dose was reduced to 85 mg once daily for subjects taking ATV/r or LPV/r as part of their BR because of known PK interactions with these agents.)

- Treatment Group 2: RAL 400 mg twice daily + EVG placebo once daily + BR (n=358)

The BR was constructed by the investigator, based on viral resistance testing, to comprise a fully active PI/r (which could be ATV/r, DRV/r, FPV/r, LPV/r, or TPV/r) and a second agent. At study sites other than those in Spain, the second agent did not need to be fully active and could be 1 NRTI or nucleotide reverse transcriptase inhibitor, the NNRTI etravirine, the CCR5 receptor inhibitor maraviroc, or the HIV-1 fusion inhibitor enfurvirtide. The second agent could not be an integrase inhibitor, the NNRTIs EFV, nevirapine, or delavirdine (because of unknown PK interactions with EVG), or the STRs Atripla (EFV/FTC/TDF) or Trizivir (ABC/3TC/ZDV). At sites in Spain the second agent was required to be fully active.

If the M184V/I RT mutation was present in the screening genotype, and an NRTI was used as the second agent, FTC or 3TC could be added as a third agent in the BR to maintain the M184V/I mutation. In this situation only, the STR therapies Combivir (3TC/ZDV), Truvada (FTC/TDF), or Epzicom/Kivexa (ABC/3TC) could be used as combined second and third agents of the BR.

The initial 96-week randomized double-blind period of Study GS-US-183-0145 has been completed, and the primary endpoint (the percentage of subjects who achieved and maintained confirmed HIV-1 RNA < 50 copies/mL through Week 48) has been analyzed {19045}.

At the time of the data cut-off for the 96-week analysis, 146 of 354 subjects (41.2%) in the EVG group and 150 of 358 subjects (41.9%) in the RAL group had discontinued study medication and 138 subjects (39.0%) in the EVG group and 135 subjects (37.7%) in the RAL group had discontinued the study. Reasons for discontinuation of study medication were generally similar in the 2 groups (principally subject noncompliance and lost to follow-up), but there were fewer deaths in the EVG group (1 subject; 0.3%) than in the RAL group (9 subjects; 2.5%).

Similar proportions of subjects in each treatment group achieved and maintained confirmed HIV-1 RNA < 50 copies/mL at Week 48, the primary efficacy endpoint, using time-to-loss-of-virologic-response (TLOVR) analysis: 59.0% of subjects in the EVG group and 57.8% of subjects in the RAL group were classified as responders. The stratum-weighted difference between treatment groups (EVG – RAL) was 1.1% (95% CI: –6.0% to 8.2%). Since the lower bound of the 2-sided 95% CI of the stratum-weighted difference in response rate (EVG – RAL) was greater than the prespecified noninferiority margin of –10%, EVG was determined to be noninferior to RAL.

Slightly more subjects were never suppressed in the EVG group (7.7%) than in the RAL group (5.1%). In contrast, a higher proportion of subjects in the RAL group (16.0%) than in the EVG group (11.4%) experienced virologic rebound. Taken together, the proportions of subjects with loss of virologic response (due to never having been suppressed or to virologic rebound) were similar in the EVG and RAL treatment groups.

At Week 96, the Kaplan-Meier estimate for the proportion of subjects with loss of virologic response was 52% in the EVG group and 55% in the RAL group. The median time to loss of virologic response was 617 days in the EVG group and 562 days in the RAL group ($p = 0.86$). Mean (SD) decreases from baseline in HIV-1 RNA were –2.26 (1.078) $\log_{10}$ copies/mL in the EVG group and –2.31 (1.068) $\log_{10}$ copies/mL in the RAL group. The difference in least-squares means was 0.05 (95% CI: –0.12 to 0.22). At Week 96, mean (SD) increases from baseline in CD4 cell count were 205 (191.5) cells/mm^3 in the EVG group and 198 (162.2) cells/mm^3 in the RAL group. The difference in least-squares means was 7 (95% CI: –25 to 39).

The 95% CIs for treatment differences in the percentages of subjects achieving and maintaining confirmed HIV-1 RNA < 50 copies/mL included zero for all subgroups analyzed (baseline HIV-1 RNA ≤/> 100,000 copies/mL, class of second agent in BR [NRTI/other], age ≤/> 45 years, male/female, white/nonwhite, US and Puerto Rico/other geographic area, baseline CD4 cell count ≤/> 200 cells/mm^3, type of PI in BR [FPV, DRV, or TPV versus LPV or ATV], and baseline genotypic sensitivity score ≤/> 1) suggesting no treatment difference across subgroups.

At screening, all subjects were analyzed for preexisting protease and RT resistance. Overall, 70% of subjects harbored at least 1 nucleoside-associated mutation, most commonly M184V/I, present in 57% of subjects. A total of 180 subjects met the virologic failure criteria during the Week 96 analysis period and were included in the resistance analysis population. The proportions of subjects in each of the treatment groups included in the resistance analysis population were similar (24.8% of subjects in the EVG group and 26.5% of subjects in the RAL group). INSTI resistance mutations occurred at similarly low frequencies in each treatment group (EVG 6.6%, RAL 7.4%). The most frequent INSTI resistance mutations observed in the EVG group were T66I/A and E92Q (in 2.3% and 2.0% of subjects, respectively), and the most frequent INSTI resistance mutations observed in the RAL group were N155H and Q148H (in 4.6% and 2.0% of subjects, respectively). Mutations T66I/A, S147G, and Q148R were found exclusively in the EVG group, while Y143R/H/C and Q148H were found exclusively in the RAL group. Mutations E92Q/G, T97A, and N155H were observed in both treatment groups, confirming their cross-resistant nature.

Postbaseline phenotypic analysis showed that 91% of subjects that developed INSTI resistance mutations while receiving RAL had phenotypic resistance to RAL. Most of these subjects exhibited cross-resistance to both RAL and EVG. Seventy percent of subjects developing INSTI resistance mutations while receiving EVG had phenotypic resistance to EVG. Only 55% of these subjects displayed cross-resistance to both drugs. Overall, the presence of genotypic resistance correlated well with the presence of phenotypic resistance, with varying degrees of cross-resistance observed depending on the specific resistance pattern.

EVG/r was well-tolerated in this study. The most frequently reported AEs in the EVG group were diarrhea (33.6%), upper respiratory tract infection (18.9%), and headache (13.3%). Adverse events were mostly mild or moderate in severity and were reported with similar frequencies in both treatment groups except for diarrhea, which was reported more frequently in the EVG group. Grade 3 or Grade 4 AEs reported for more than 1% of subjects in either treatment group were: pneumonia (EVG: 1.7%, 6 subjects; RAL: 1.4%, 5 subjects); cellulitis (EVG: 1.1%, 4 subjects; RAL: 0.3%, 1 subject); blood bilirubin increased, diarrhea, and hypercholesterolemia (each reported for EVG: 0.3%, 1 subject; RAL: 1.1%, 4 subjects); and liver function test abnormal (EVG: 0 subjects; RAL: 1.4%, 5 subjects).

Nine subjects died during the Week 96 analysis period, 2 in the EVG group and 7 in the RAL group. Neither death in the EVG group (due to acute myocardial infarction and rectal hemorrhage) was considered by the investigator to be related to study drug. Three additional deaths, 1 in the EVG group (due to chronic hepatic failure as a result of hepatitis C) and 2 in the RAL group (due to Stage IV Hodgkin's lymphoma, and cardiomegaly with mitral valve prolapse) were not treatment-emergent in that they occurred > 30 days after the last dose of study drugs, and were not considered by the investigator to be related to study drug. Similar proportions of subjects in each treatment group reported SAEs (EVG 20.1%, RAL: 23.5%) and SAEs judged by the investigator to be related to study drug (EVG: 1.1%, 4 subjects; RAL: 2.0%, 7 subjects) during the Week 96 analysis period. SAEs reported for > 1% of subjects in either treatment group were:

- EVG group: pneumonia (3.4%, 12 subjects), and cellulitis (1.4%, 5 subjects)

- RAL group: pneumonia (2.0%, 7 subjects); bronchitis, cellulitis, chest pain, and suicidal ideation (each 1.1%, 4 subjects)

Similar proportions of subjects in each treatment group discontinued study drug due to an AE during the Week 96 analysis period (EVG: 3.1%, 11 subjects; RAL 4.2%, 15 subjects). Adverse events leading to study drug discontinuation for more than 1 subject were nausea (EVG 2 subjects), vomiting (EVG 2 subjects), and hepatitis/acute hepatitis (RAL 3 subjects). Adverse events considered related to study drug by the investigator leading to study drug discontinuation were reported for 6 subjects (1.7%) in the EVG group and 9 subjects (2.5%) in the RAL group.

In clinical studies in adult HIV-infected subjects completed to date, EVG/r was generally well tolerated at all dose levels and with all concomitant treatments studied, as demonstrated by the low overall rate of study drug discontinuation due to AEs and the mild/moderate severity of most AEs. The most frequently reported AEs for HIV-1 infected subjects receiving an EVG-containing regimen were diarrhea, upper respiratory tract infection, and headache.

1.2.3.5. Clinical Trials in HIV-1 Infected Pediatric Subjects

Study GS-US-183-0152 was a Phase 1B, nonrandomized, open-label, multicenter study of once-daily administration of EVG plus an ARV BR containing a PI/r that comprised a 10-day PK evaluation phase followed by an optional treatment phase through 48 weeks. The PK phase evaluated the steady-state pharmacokinetics of EVG; the optional treatment phase evaluated safety and efficacy through 48 weeks of treatment. Twenty-five eligible subjects ages 12 to < 18 years were assigned to 1 of 2 EVG dose groups (150 mg/day or 85 mg/day) according to the PI prescribed for the BR. All subjects received their RTV dose based on the dosing schedule prescribed for the PI; no additional RTV was required to be taken with EVG.

- Group 1: EVG 150 mg plus DRV/r, FPV/r, or TPV/r (n=11)

- Group 2: EVG 85 mg plus LPV/r or ATV/r (n=14)

Two subjects (1 in each treatment group) did not complete the study because of AEs during the 10-day PK evaluation phase of the study. Eleven of the 23 subjects who completed the 10-day PK evaluation phase of the study were eligible for enrollment in the optional treatment phase; 9/11 eligible subjects enrolled in the optional treatment phase, each of whom completed treatment through 48 weeks. Of the 25 enrolled subjects, 13 (52.0%) were male, 7 (28.0%) were white, and 18 (72.0%) were African-American. The median age was 16 years (range 12 to 17 years: 80% 15 to < 18 years; 48% Tanner Stage 5).

The mean steady-state value for EVG C_{tau} on Day 10 was higher in the 85-mg treatment group (627.0 ng/mL) than in the 150 mg treatment group (324.5 ng/mL), consistent with EVG 85-mg versus EVG 150-mg data from adult studies. Protocol-defined statistical

comparison indicated that the geometric least squares-means ratio (90% CI) in adolescents versus adult healthy subjects for EVG 150 mg AUC_{tau} (93.43 [75.81, 115.14]) was within predefined equivalence boundaries.

Exploratory statistical comparisons of exposure between EVG 150 mg in adolescents and EVG 150 mg in adult HIV-1 infected subjects indicated comparable EVG AUC_{tau} and C_{tau} and a modest difference in C_{max}. The EVG 85-mg adolescent dose provided modestly higher AUC_{tau} and C_{max} compared to EVG 150-mg adult data. These differences are not considered to be clinically relevant based on the favorable long-term safety profile for EVG in adults at doses up to 300 mg once daily (Study GS-US-183-0130).

Overall, statistical comparisons between HIV-1 infected adolescents and healthy or HIV-1 infected adults indicated comparable and clinically equivalent EVG exposures. EVG/r mean C_{tau} was 7- to 13-fold above the in vitro protein binding-adjusted IC_{95} (45 ng/mL).

At the end of the 10-day PK evaluation phase, all 11 evaluable subjects who had a baseline HIV-1 RNA level > 1000 copies/mL at screening had reductions from baseline in HIV-1 RNA (median -1.84 $\log_{10}$ copies/mL, range –2.41 to –1.39 $\log_{10}$ copies/mL). Nine of 11 eligible subjects (screening plasma HIV-1 RNA level > 1000 copies/mL) subsequently enrolled in, and completed, the 48-week optional treatment phase. All 9 subjects had reductions in HIV-1 RNA from baseline to Week 48 (the median change from baseline was -1.74 $\log_{10}$ copies/mL, range –2.69 to –0.40), and 2 subjects had HIV-1 RNA < 50 copies/mL at Week 48. Increases were observed in CD4 cell counts and percentages; 6/9 subjects had a CD4 cell count within or near the normal reference range at Week 48, and 6/9 subjects had CD4 cell percentage values within or near the normal reference range at Week 48.

Four of 9 subjects enrolled in the optional treatment phase through 48 weeks were included in the resistance analysis population. Three subjects had preexisting secondary integrase mutations at baseline (V72I, L74M, and S119G), and 1 subject developed a secondary integrase resistance mutation at or before Week 48 (V72I); however, all 4 subjects lacked primary integrase resistance mutations and remained phenotypically susceptible to EVG (fold-change < 2.5).

All 25 enrolled subjects received at least 1 dose of EVG. Twenty-three of 25 subjects completed the 10-day PK evaluation phase of the study, including 13/14 subjects in the EVG 85-mg treatment group and 10/11 subjects in the EVG 150-mg treatment group. The 9 subjects participating in the optional treatment phase of the study received a median 48.3 weeks of EVG (range 47.6 weeks to 49.6 weeks).

During the 10-day PK evaluation phase of the study, treatment-emergent AEs were reported for 10/14 subjects (71.4%) in the EVG 85-mg treatment group and 8/11 subjects (72.7%) in the EVG 150-mg treatment group. Overall, nausea (6/25 subjects, 24.0%) and dizziness (3/25 subjects, 12.0%) were the most frequently reported AEs; all other AEs were reported for 2 or fewer subjects in either treatment group.

Most AEs were mild or moderate in severity (Grade 1 or 2) and considered by the investigator to be not related to study treatment. Grade 3 was the highest severity AE reported during the 10-day PK evaluation phase of the study; Grade 3 AEs were reported in 2/25 subjects, 1 in each treatment group, and included treatment-related nausea, vomiting, dizziness and chills. Both of these subjects discontinued EVG because of the AEs. No additional subject prematurely discontinued EVG. There were no deaths. There was 1 SAE (pneumonia not related to study drug).

No Grade 3 or 4 AEs and no SAEs were reported for the 9 subjects enrolled in the optional treatment phase through 48 weeks. No relationship between AE frequency and EVG dose was observed.

There was no apparent study treatment-related change over time in hematology, clinical chemistry, urinalysis, or safety serology results. One subject in the EVG 85-mg treatment group (whose background regimen included ATV/r) had Grade 3 hyperbilirubinemia on Day 14, during the posttreatment follow-up period. All 9 subjects enrolled in the optional treatment phase of the study had treatment-emergent graded laboratory abnormalities at some time point through 48 weeks; most of these laboratory abnormalities were Grade 1 or 2. No notable change in vital signs, ECGs, or physical findings was observed during the study. No pregnancy occurred during the study.

1.3. Rationale for This Study

Although more than 20 different antiretrovirals in five classes are available for the treatment of HIV infection in adults, treatment-experienced pediatric patients who experience virologic failure continue to have limited treatment options. Children with longstanding HIV infection are in particular need of new classes of drugs that are active against HIV resistant to existing classes of agents. Currently, HIV-infected children have very limited options for well-tolerated once daily therapy. No once daily INSTI is currently approved for use in HIV-1 infected children.

Thus, for many children who have experienced and/or failed treatment there is currently unmet medical need for effective therapies to be included in second and later-line regimens.

Elvitegravir is an HIV-1 integrase inhibitor that has demonstrated in vitro activity against NNRTI, NRTI or PI drug resistant HIV-1. In clinical studies, elvitegravir has produced significant declines in HIV-1 RNA in treatment-experienced patients with documented drug resistance.

The current study is designed to examine the pharmacokinetics, safety and antiviral activity of elvitegravir added to a BR containing a ritonavir-boosted PI in HIV-1 infected, antiretroviral treatment-experienced pediatric subjects.

1.4. Rationale for the Current Dose

Phase 1 and 2 studies have investigated a wide range of doses, dosing intervals, and drug exposures, including a > 6-fold range in dose and > 8-fold range in mean trough concentrations and indicate that elvitegravir (GS-9137) trough (C_{min}) is associated with antiviral activity. Analyses of these exposure-response data indicate that the 125 mg boosted dose of elvitegravir provides exposures with substantial and perhaps optimal antiviral activity {9320}, {10590}.

Elvitegravir administered to pediatric subjects within the weight range evaluated in this study is planned to provide plasma exposures comparable to the EVG exposures achieved in adults when coadministered with a PI/r. The EVG dose is intended to be adjusted appropriately depending on the ritonavir boosted PI being administered. EVG is currently available as 50 mg, 85 mg and 150 mg tablets, as well as a powder for oral suspension formulation. The proposed doses take into account the available dosage forms. The oral suspension formulation (150 mg dose) and the pediatric tablets (3 x 50 mg dose) show bioequivalent exposures versus the adult tablet formulation.

The doses of elvitegravir administered to the adolescent population are identical to the doses administered in the adult Phase 3 study: EVG 150 mg when coadministered with darunavir/r, fosamprenavir/r or tipranavir/r, and EVG 85 mg when coadminstered with atazanavir/r or lopinavir/r. These doses have been demonstrated to result in EVG exposures in HIV-infected adolescents that are comparable and clinically equivalent to exposures in healthy or HIV-1 infected adults (Study GS-US-183-0152).

EVG dose selection in combination with the ritonavir-boosted protease inhibitors DRV, TPV, fAPV, ATV, or LPV entailed considerations of the differing adult EVG dose with these agents (EVG 150 mg with DRV, TPV or fAPV; and EVG 85 mg with LPV or ATV) and the different PI/r dose across pediatric weight bands that are unique to each PI/r. The proposed EVG doses in combination with DRV/r, TPV/r and fAPV/r across the weight bands are listed in (Table 1-3). The proposed EVG doses in combination with ATV/r or LPV/r, across the weight bands are listed in (Table 1-4).

For drugs with extensive hepatic metabolism, such as EVG, a prolonged elimination half-life is generally observed in neonates compared with older age groups {14699}. Therefore, these drugs, including EVG, should be administered with caution until subjects have reached the age of 2 months {10609}. PK data for LPV/r in infants ~ 6 weeks of age as well as fAPV in infants < 6 months of age demonstrate lower exposure for the PI in infants of these ages compared with older children {21225}, {12272}. Based on the additional uncertainty for a dose-exposure relationship in children < 2 months old, EVG administration will be restricted to coadministration with LPV/r, and subjects will be enrolled individually and dosed sequentially within the cohort following PK analysis and confirmation of the selected dose of the previous subject(s).

The EVG doses proposed for this study represent a higher dose on a mg/kg basis relative to the adult dose, with the magnitude of increase comparable to that of the corresponding PI within each weight band. Overall, EVG exposures with the various PIs at the various doses are expected to be comparable to those observed in adults and are expected to result in efficacious plasma concentrations, i.e. EVG C_{trough} maintained above the IC_{95} (44.5 ng/mL; protein-binding adjusted). If suitable EVG exposures are not observed in the PK-lead-in phase within an age cohort, alternate EVG dose(s) may be evaluated.

Table 1-3. EVG dose (mg) by Weight Range with DRV, fAPV or TPV

Weight range	EVG dose (mg) w DRV, fAPV or TPV	mg/kg
≥34 kg	150	<4.4
≥28 to <34 kg	100	2.9-3.6
≥17 to <28 kg	85	3.0-5.0
<17 kg	-[a]	4

a For subjects weighing <17 kg, EVG dose will be calculated based on the subject's actual weight to provide 4 mg/kg.

Table 1-4. EVG dose (mg) by Weight Range with ATV, LPV

Weight range	EVG dose (mg) w ATV, LPV	mg/kg
≥30 kg	85	<2.8
≥17 to <30 kg	50	1.7-2.8
<17 kg	-[a]	2.4

a For subjects weighing <17 kg, EVG dose will be calculated based on the subject's actual weight to provide 2.4 mg/kg.

The decision of which ritonavir-boosted PI is selected as part of the BR is strictly at the discretion of the investigator in accordance to the local standard of care. Due to the availability of drug-drug interaction data with elvitegravir, the following ritonavir-boosted PIs are allowed to be prescribed by the investigator as part of the BR: atazanavir/r, darunavir/r, fosamprenavir/r, lopinavir/r (Kaletra), or tipranavir/r (Refer to Section 5.3; no other marketed PIs may be taken as part of the BR due to unknown potential pharmacokinetic interactions). All subjects who enroll will receive at least two fully-active antiretroviral agents one of which must be a fully-active ritonavir-boosted PI. Subjects must take the ritonavir dose prescribed for the PI that is part of the BR. No additional ritonavir is required to be taken with elvitegravir. Elvitegravir should be administered once daily at the same time as a once-daily dose of the ritonavir-boosted PI, or with the first dose of a twice-daily ritonavir-boosted PI with food at the same time each day.

1.5. Compliance

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

2. OBJECTIVES

The primary objectives of this study are:

- To evaluate the steady-state PK and confirm the dose of EVG/r in HIV-1 infected, antiretroviral treatment-experienced subjects 4 weeks to <18 years of age
- To evaluate the safety and tolerability of EVG/r in HIV-1 infected, antiretroviral treatment-experienced subjects 4 weeks to <18 years of age

The secondary objective of this study is:

- To evaluate the antiviral activity of EVG/r in HIV-1 infected, antiretroviral treatment-experienced subjects 4 weeks to <18 years of age who are failing their current HAART regimen

3. STUDY DESIGN

3.1. Endpoints

The primary endpoints of this study are:

- PK parameters AUC_{tau} and C_{max} of EVG
- The incidence of treatment-emergent AEs and treatment-emergent laboratory abnormalities

The secondary endpoints of this study are:

- PK parameters C_{tau}, CL/F, and Vz/F of EVG
- The percentage of subjects with plasma HIV-1 RNA <50 and <400 copies/mL at Weeks 24 and 48 as defined by the FDA snapshot analysis, respectively
- The change from baseline in plasma log_{10} HIV-1 RNA (copies/mL), in CD4+ cell count (cells/μL), and CD4 percentage at Weeks 24 and 48
- Tanner Stages at Weeks 24 and 48, and age of first menses.
- Palatability of oral suspension formulation of EVG in appropriate age group
- Adherence to EVG

3.2. Study Design

This protocol describes an open-label, multicohort, two-part study evaluating the PK, safety, and antiviral activity of EVG administered with a BR containing a PI/r in HIV-1 infected, antiretroviral treatment-experienced pediatric subjects.

Up to approximately 86 pediatric subjects 4 weeks to <18 years of age will be enrolled to receive EVG administered with a BR containing PI/r and other BR components. The study will proceed in 2 parts (Part A and Part B), as follows:

Part A

Approximately 36 subjects with either suppressed viremia (HIV-1 RNA <50 copies/mL) or failing a current antiretroviral regimen (HIV-1 RNA >1,000 copies/mL) will be enrolled to evaluate the steady state PK and confirm the dose of EVG. Only subjects aged 4 weeks to < 12 years old will be enrolled in this part.

Subjects will be enrolled sequentially by cohort* as follows:

- **Cohort 2:** 6 to < 12 years old (n ≥ 12)
- **Cohort 3:** 2 to < 6 years old (n ≥12)
- **Cohort 4:** 4 weeks to < 2 years old (n ≥12), which will consist of the following age subgroups:
  - **Cohort 4a:** 6 months to < 2 years old (n ≥ 8)
  - **Cohort 4b**:** 4 weeks to < 6 months old (n ≥ 4)

*Cohort 1 subjects are aged 12 to < 18 years old. No subjects will be enrolled in this age group for Part A as EVG PK data are already available.

**Based on the uncertainty for a dose-exposure relationship in subjects < 2 months old, EVG administration will be restricted to coadministration with lopinavir/r, and subjects will be enrolled individually and dosed sequentially within the cohort following PK analysis and confirmation of the selected dose of the previous subject(s).

Part A will be enrolled sequentially by age cohort. Enrollment will be limited to Cohort 2 in Part A until EVG safety and PK through Day 10 have been analyzed and determined to be acceptable in subjects aged 6 to < 12 years old. Upon review of safety and PK data in Cohort 2, enrollment will then be limited to Cohort 3 until EVG safety and PK through Day 10 have been analyzed and determined to be acceptable in subjects aged 2 to < 6 years old. Upon review of safety and PK data in Cohort 3, enrollment will then be limited to Cohort 4a until EVG PK through Day 10 and safety through Week 12 have been analyzed and determined to be acceptable in subjects aged 6 months to < 2 years old. Subsequently, Part A enrollment will open for Cohort 4b.

All subjects enrolled in Part A will participate in an **Intensive PK evaluation of EVG on Day 10.** For Cohorts 2 and 3, samples will be collected at 0 (predose, ≤ 30 minutes), 1.5, 2.5, 3.5, 5, 8, 10, and 12 hours postdose. For Cohort 4, samples will be collected at 0 (predose, ≤ 30 minutes), 3, 3.5, 5, and 8 hours postdose. Microsampling of intensive PK timepoints will be implemented for subjects in Cohort 4.

Replacement subjects may be enrolled for subjects whose intensive PK data is not evaluable or who do not complete all intensive PK procedures in Part A for reasons other than discontinuation due to treatment-related adverse events. Replacement subjects will not be enrolled in Part A for subjects who discontinue the study due to treatment-related adverse events. Subject diary cards will be provided to all Part A subjects and/or parents/guardians to record study drugs administration on Days 6-9 prior to the Day 10 Intensive PK visit.

EVG therapeutic dose confirmation will be established if the 90% CI of the geometric mean ratio of EVG AUC between the pediatric versus historical EVG exposures are within the

bounds of 70-143%. If a subject has EVG C_{tau} levels <44.5 ng/mL and has documented compliance to study drug, the subject will be discontinued.

Subjects with HIV-1 RNA <50 copies/mL at screening are considered to have suppressed viremia and will discontinue EVG following the Day 10 intensive PK visit. Subjects will be required to return to the clinic 30 days after completion of the Day 10 intensive PK visit for a 30-Day Follow-Up Visit.

Subjects with HIV-1 RNA >1,000 copies/mL at screening are considered to be failing their antiretroviral regimen and will continue to receive EVG following completion of the Day 10 intensive PK visit and will return for scheduled study visits. Data from these subjects will be combined with data from Part B of the study.

Part B

Up to 50 subjects who are failing a current antiretroviral regimen (HIV-1 RNA >1,000 copies/mL) will be enrolled in Part B to evaluate the safety, tolerability and antiviral activity of EVG. The number of additional subjects to be enrolled in Part B will depend on the number of subjects with HIV-1 RNA >1,000 copies/mL enrolled in Part A who continue EVG therapy beyond Day 10. Overall, a total of 50 subjects in Part A and B combined are planned to complete 48 weeks of EVG therapy.

For Cohort 1 (12 to <18 year olds), screening in Part B will initiate in parallel with screening in Part A. For Cohorts 2, 3 and 4 in Part B, additional subjects will be screened and initiated sequentially by each age cohort following confirmation of appropriate EVG exposure from the corresponding age cohort in Part A.

Subjects will be enrolled sequentially by cohort as follows:

- **Cohort 1:** 12 to < 18 years old ($n \geq 8$)
- **Cohort 2:** 6 to < 12 years old ($n \geq 8$)
- **Cohort 3:** 2 to < 6 years old ($n \geq 8$)
- **Cohort 4***:** 4 weeks to < 2 years old ($n \geq 4$)

***Subjects younger than 6 months will not be allowed to enroll in Part B until Part A Cohort 4b data are available indicating acceptable EVG safety and PK through Day 10 in this age group.

For All Subjects (Parts A and B)

Laboratory analyses (hematology, chemistry, and urinalysis), HIV-1 RNA (Roche COBAS TaqMan v2.0), CD4+ cell count and percentage, vital signs, complete or

symptom-directed physical examinations and estimated GFR using the Schwartz formula will be performed at Screening, Baseline, and all subsequent in-clinic study visits.

HBV and HCV serologies will be analyzed (with the exception of Cohorts 3 and 4, where maternal medical history for HBV and HCV will be obtained in lieu of laboratory testing) and supine ECG will be performed at the Screening visit.

For subjects failing a current antiretroviral regimen (HIV-1 RNA >1,000 copies/mL), HIV-1 integrase, protease, and reverse transcriptase genotype will be analyzed at Screening using the GenoSure PRIme assay (Monogram Biosciences, Inc.).

Subjects enrolled in Part A with HIV-1 RNA <50 copies/mL at screening (with suppressed viremia) will return for the Day 10 Intensive PK evaluation and discontinue the study after Day 10. A telephone visit wll occur on Week 1 (Day 7) for safety follow-up assessments.

Subjects enrolled in Part A who are failing a current antiretroviral regimen (HIV-1 RNA >1,000 copies/mL) and all subjects enrolled in Part B will return for study visits at Weeks 4, 8, 12, 16, and then every 8 weeks through Week 48. A telephone visit wll occur on Week 1 (Day 7) and Week 3 for safety follow-up assessments.

Metabolic assessments (glucose and lipid panel [total cholesterol, HDL, direct LDL, and triglycerides]) will be assessed at Baseline, Week 24, and Week 48 for subjects failing a current antiretroviral regimen (HIV-1 RNA >1,000 copies/mL) and weighing at ≥ 13 kg at the time of the visit.

Tanner Stage assessments (Appendix 6) will be performed for subjects ≥ 6 years of age at the time of the visit, at Baseline, Weeks 24 and 48. Once a subject is determined to be Tanner Stage 5, Tanner Stage assessments will no longer be performed.

Palatability of EVG suspension formulation will be assessed at Baseline, Day 10 (**Part A only**), Week 24, and Week 48, as applicable.

At Weeks 16 and 40, a trough PK sample (20 to 24 hours postdose) will be collected. A random single plasma PK sample will be collected at Weeks 4, 8, 12 (except for Cohort 3), and 32, for descriptive PK.

Resistance testing will be performed in subjects who experience suboptimal response, virologic rebound, and in subjects at Week 48 or ESDD visit if HIV-1 RNA is ≥ 400 copies/mL.

Adverse events and concomitant medications will be assessed at each visit. Treatment adherence will be assessed at all post Baseline visits.

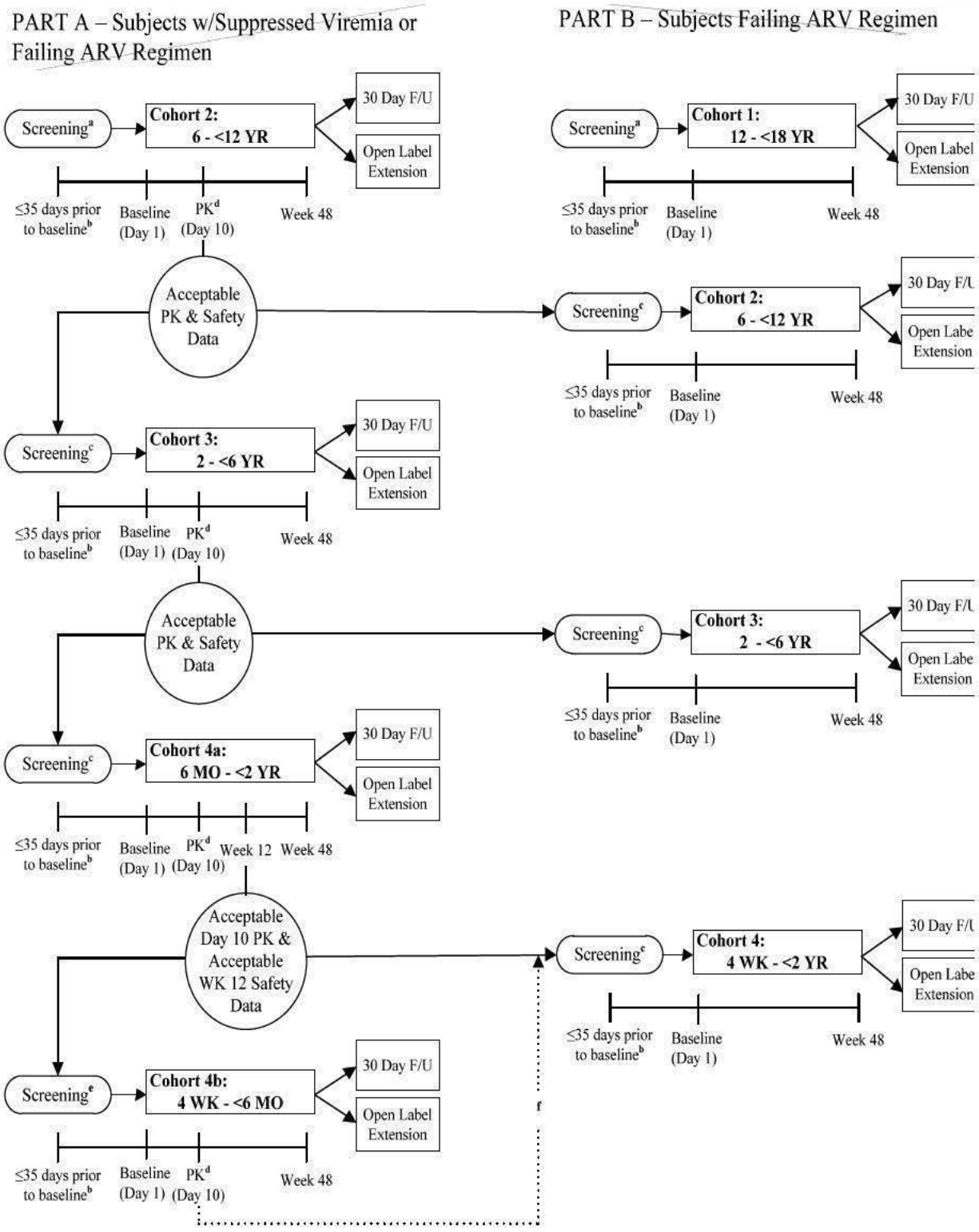
Subjects who are permanently discontinued from the study before Week 48 will be required to complete an ESDD visit within 72 hours of stopping study drug and return to the clinic 30 days after the ESDD visit for a 30-Day Follow-Up Visit.

After Week 48, all subjects receiving EVG will be given the option to participate in an extension phase of the study where Gilead will provide EVG until: a) the subject turns 18 and EVG is available for use in adults in the country in which the subject is enrolled or b) the age appropriate EVG formulation becomes available for use in the country in which the subject is enrolled or c) Gilead Sciences elects to terminate development of EVG in the applicable country. Subjects who are eligible to participate in the study extension must demonstrate evidence of response to EVG or show absence of resistance to EVG for subjects with HIV-1 RNA > 400 copies/mL at Week 48.

Subjects who complete the study through Week 48 and do not wish to participate in the study extension will be required to return to the clinic 30 days after completion of the Week 48 visit for a 30-Day Follow-Up Visit.

In the extension phase of the study, subjects will return for study visits every 12 weeks for laboratory analyses (hematology, chemistry and urinalysis), HIV-1 RNA (Roche COBAS TaqMan v2.0), CD4+ cell count and percentage, vital signs, symptom-directed physical examinations and estimated GFR using the Schwartz formula. Metabolic assessments (glucose and lipid panel [total cholesterol, HDL, direct LDL, and triglycerides]) will be assessed every 48 weeks for subjects failing a current antiretroviral regimen (HIV-1 RNA >1,000 copies/mL) and weighing at ≥ 13 kg at the time of the visit. Tanner Stage assessments (Appendix 6) will be performed for subjects ≥ 6 years of age at the time of the visit, for every 48 weeks in the extension phase. Once a subject is determined to be Tanner Stage 5, Tanner Stage assessments will no longer be performed. A random single plasma PK sample will be collected every 12 weeks for descriptive PK.

Figure 3-1. Study Schema



a Occurs concurrently

b The screening window may be extended to 42 days for subjects who require repeat testing of HIV-1 genotype or if the screening visit is divided into multiple visits.

c Screening will initiate after analysis of Day 10 PK and confirmation of EVG exposure in the previous age cohort.

d Subjects with suppressed viremia will discontinue EVG following completion of Day 10 PK and will complete the study following the Day 30 follow-up visit.

e Screening for Part A Cohort 4b will initiate **only after Day 10 PK and safety through Week 12** have been analyzed and determined to be acceptable in Cohort 4a.

f Subjects < 6 months of age will not be allowed to enroll in Part B until Part A Cohort 4b data are available indicating acceptable EVG safety and PK through Day 10.

3.3. Study Treatments

EVG 50 mg, 85 mg, and 150 mg tablets or EVG powder for oral suspension formulation (5 mg/mL) will be administered orally with food in combination with a BR. Allowed and disallowed BR agents are as follows:

- For subjects with HIV-1 RNA <50 copies/mL at screening, EVG will be added to the existing BR that must include a PI/r. The dose of EVG will be dependent upon the co-administered PI/r and will be based on body weight.

- For subjects with HIV-1 RNA >1,000 copies/mL at screening, EVG will be added to a newly constructed BR selected by the investigator that is based on the subject's antiretroviral history and screening or historical viral resistance results. The BR must include at least 2 fully-active agents, one of which is a fully-active PI/r (fully-active PI/r is defined by genotypic analysis).

The PI/r contained in the background regimen must be one of the following: lopinavir/r (Kaletra), atazanavir/r, darunavir/r, tipranavir/r, or fosamprenavir/r. For subjects < 2 months old, only lopinavir/r is allowed. The BR may contain additional antiretrovirals except for the following: saquinavir, indinavir, nelfinavir, double PI regimens, efavirenz, nevirapine, delavirdine or an integrase strand transfer inhibitor. All PI should be administered according to local product label.

All subjects must take their ritonavir dose based on the dosing schedule prescribed for the PI; no additional ritonavir is required to be taken with EVG.

For subjects weighing ≥ 17 kg and receiving darunavir/r, tipranavir/r or fosamprenavir/r, the EVG dose will be as follows:

- 85 mg for subjects ≥ 17 kg to < 28 kg

- 100 mg for subjects ≥ 28 kg to < 34 kg

- 150 mg for subjects ≥ 34 kg

For subjects weighing ≥ 17 kg and receiving atazanavir/r or lopinavir/r, the EVG dose will be as follows:

- 50 mg for subjects ≥ 17 kg to < 30 kg

- 85 mg for subjects ≥ 30 kg

Note: For subjects who are not able to swallow tablets, EVG powder for oral suspension formulation (5 mg/mL) may be administered to obtain EVG doses of 50 mg, 85 mg, 100 mg, or 150 mg.

For subjects weighing < 17 kg and receiving darunavir/r, tipranavir/r or fosamprenavir/r, the EVG dose will be 4 mg/kg, and for subjects weighing < 17 kg and receiving lopinavir/r or atazanavir/r, the EVG dose will be 2.4 mg/kg, using the EVG powder for oral suspension formulation (5 mg/mL) administered as an oral suspension.

Please refer to Section 5.3, Table 5-1, Table 5-2, Table 5-3, and Table 5-4 for detailed information.

3.4. Duration of Treatment

The screening period will be up to 35 days (42 days if genotype retest is required or if the screening visit is divided into multiple visits). The treatment periods are as follows:

- Up to 10 days for subjects with HIV-1 RNA <50 copies/mL at screening
- Up to 48 weeks for subjects with HIV-1 RNA >1,000 copies/mL at screening, and longer if subjects elect to participate in an extension phase of the study where Gilead will provide EVG until: a) the subject turns 18 and EVG is available for use in adults in the country in which the subject is enrolled or b) the age appropriate EVG formulation becomes available for use in the country in which the subject is enrolled or c) Gilead Sciences elects to terminate development of EVG in the applicable country.

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.
- 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
- Therapeutic failure (ie, virologic failure, see Section 6.8 for details)
- Subject request to discontinue for any reason
- Subject noncompliance
- Pregnancy during the study; refer to Section 7.8
- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC)

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Up to 86 pediatric subjects 4 weeks to <18 years of age are planned to be enrolled into this study. For Part A, approximately 36 evaluable subjects are planned to be enrolled. For Part B, between 14 and 50 subjects, **depending** on the number of subjects with HIV-1 RNA >1,000 copies/mL at screening enrolled in Part A who continue EVG therapy beyond Day 10, are planned to be enrolled.

In Part A, replacement subjects may be enrolled for subjects whose intensive PK data is not evaluable or who do not complete all intensive PK procedures for reasons other than discontinuation due to treatment-related adverse events. Replacement subjects will not be enrolled in Part A for subjects who discontinue the study due to treatment-related adverse events.

4.2. Inclusion Criteria

Subjects must meet **all** of the following inclusion criteria to be eligible for participation in this study. Subjects with screening results that do not meet eligibility criteria will not be allowed to rescreen, with the exception of exclusionary screening laboratory results as indicated in Section 6.2.1.

4.2.1. HIV-1 infected male and female subjects 4 weeks (gestational age of at least 44 weeks) to < 18 years of age at the Baseline visit (according to Cohort).

4.2.2. Subjects are able to provide written assent if they have the ability to read and write.

4.2.3. Parent or legal guardian able to provide written informed consent prior to any screening evaluations and willing to comply with study requirements.

4.2.4. Body weight at screening as follows:

- Cohort 2 – greater than 15 kg
- Cohort 3 – greater than 10.6 kg
- Cohort 4 – greater than 5 kg

4.2.5. Adequate renal function: Estimated Glomerular Filtration Rate (eGFR) ≥ 90 mL/min/1.73m^2 using the Schwartz Formula {23903}:

Schwartz Formula (mL/min/1.73m^2) = k × L/S_{Cr} (k is a proportionality constant, for pediatric male/female infants to < 2 years old, k = 0.45; ≥ 2 years old to < 12 years old, k = 0.55; females ≥ 12 years, k = 0.55 and males ≥ 12 years, k = 0.70); L is height in centimeters (cm); and S_{Cr} is serum creatinine (mg/dL)

4.2.6. Adequate hematologic function defined as:

- Absolute neutrophil count > 500 cells/mm^3 (**Note:** Subjects with chronic neutropenia, defined as having an ANC of < 500/mm^3 documented at least twice within 6 months of screening, and in whom, according to the investigator, there is no evidence of active opportunistic or serious infection can enroll in the study contingent upon approval from the Gilead Medical Monitor.)
- Hemoglobin > 8.5 g/dL (9.5 g/dL for infants less than 35 days of age)
- Platelets > 50,000/mm^3

4.2.7. Hepatic transaminases (AST and ALT) ≤ 5 x upper limit of normal (ULN)

4.2.8. Total bilirubin ≤ 1.5 mg/dL, or normal direct bilirubin

4.2.10. Negative serum β-HCG pregnancy test for female subjects (of childbearing potential only, as defined in Section 7.8).

4.2.11. For subjects with evidence of suppressed viremia **(Part A only)**:

- Plasma HIV-1 RNA concentration (at least 2 consecutive measurements) at an undetectable level according to the assay being used for at least 3 months prior to screening, and HIV-1 RNA <50 copies/mL (Roche COBAS TaqMan v2.0) at screening.
- Stable antiretroviral regimen including one of the following PI/r for at least 3 months prior to screening: lopinavir/r (Kaletra), atazanavir/r, darunavir/r, tipranavir/r, or fosamprenavir/r. Subjects undergoing dose modifications to their antiretroviral regimen for growth or switching medication formulations are considered to be on a stable antiretroviral regimen.

4.2.12. For subjects failing a current antiretroviral regimen at study entry **(Parts A and B)**:

- HIV-1 RNA >1,000 copies/mL at screening (Roche COBAS TaqMan v2.0).
- Prior treatment for HIV-1 infection, defined as 6 months of antiretroviral treatment experience (with the exception of Cohort 4 where less than 6 months of treatment experience is acceptable) and at least 1 documented resistance mutation as defined by current IAS-USA Guidelines. These resistance gene mutations must be documented in a historical genotype report(s), or in the genotype report at screening provided by Gilead Sciences.

- Stable antiretroviral regimen (or no antiretroviral regimen) for at least 30 days prior to screening. Subjects undergoing dose modifications to their antiretroviral regimen for growth or switching medication formulations are considered to be on a stable antiretroviral regimen.

- Screening genotype must show full sensitivity to EVG.

- Ability to construct a BR that must contain one of the following fully active PI/r: lopinavir/r (Kaletra), atazanavir/r, darunavir/r, tipranavir/r, or fosamprenavir/r. (Fully active is defined by genotypic analysis.)

- Genotypic sensitivity score (GSS) of at least 2 (including the fully active PI/r and EVG).

- No opportunistic infection within 30 days of study entry.

4.2.13. Male and female subjects of childbearing potential (as defined in Section 7.8) must agree to utilize highly effective contraception methods while on study treatment or agree to abstain from heterosexual intercourse throughout the study period and for 30 days following the last dose of study drug; highly effective methods normally utilize two separate forms of contraception, one of which must be an effective barrier contraceptive method. Pre-pubertal females (Tanner Stages 1 and 2 are not considered to be of childbearing potential, unless onset of menarche has occurred. See Section 7.8 for definition of females of childbearing potential).

- 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. It is recommended that an oral contraceptive contain at least 30 μg of ethinyl estradiol if administered with EVG.

4.2.14. Must be willing and able to comply with all study requirements.

4.3. Exclusion Criteria

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

4.3.1. Subjects with the following CD4+ cell counts:

- For Cohorts 1 and 2: Screening CD4+ cell count < 50 cells/mm^3

- For Cohort 3: Screening CD4+ cell count < 75 cells/mm^3

- For Cohort 4: Screening CD4+ cell count < 200 cells/mm^3

4.3.2. An acquired immunodeficiency syndrome (AIDS)-defining condition with onset within 30 days prior to screening (refer to Appendix 7)

4.3.3. Life expectancy of < 1 year

4.3.4. For subjects with HIV-1 RNA >1,000 copies/mL at screening, prior treatment of any duration with an integrase strand transfer inhibitor.

4.3.5. An ongoing serious infection requiring systemic antibiotic therapy at the time of screening.

4.3.6. Evidence of active pulmonary or extra-pulmonary tuberculosis disease:

- Within 3 months of the Screening visit for all subjects 6 months of age or older
- At any time for subjects younger than 6 months

4.3.7. Anticipated requirement for rifamycin treatment while participating in the study. **Note:** prophylactic isoniazid therapy for latent TB is allowed.

4.3.8. Have any serious or active medical or psychiatric illness which, in the opinion of the Investigator, would interfere with subject treatment, assessment, or compliance with the protocol. This would include **uncontrolled** renal, cardiac, hematological, hepatic, pulmonary (including chronic asthma), endocrine (e.g., diabetes), central nervous, gastrointestinal (including an ulcer), vascular, metabolic (thyroid disorders, adrenal disease), immunodeficiency disorders, active infection, or malignancy that are clinically significant or requiring treatment within 30 days prior to the study dosing.

4.3.9. Subjects experiencing decompensated cirrhosis (eg, ascites, encephalopathy)

4.3.10. A history of or ongoing malignancy other than cutaneous Kaposi's sarcoma (KS), basal cell carcinoma, or resected, non-invasive cutaneous squamous carcinoma. Subjects with biopsy-confirmed cutaneous KS are eligible, but must not have received any systemic therapy for KS within 30 days of Baseline and are not anticipated to require systemic therapy during the study.

4.3.11. Pregnant or lactating subjects.

4.3.12. Current alcohol or substance abuse judged by the Investigator to potentially interfere with subject compliance.

4.3.13. Have history of significant drug sensitivity or drug allergy.

4.3.14. Known hypersensitivity to the investigational medicinal product (IMP), the metabolites, or formulation excipients.

4.3.15. Have previously participated in an investigational trial involving administration of any investigational agent within 30 days prior to the study dosing.

4.3.16. Participation in any other clinical trial without prior approval from sponsor is prohibited while participating in this trial.

4.3.17. Subjects receiving ongoing therapy with any medication that is not to be taken with EVG or a component of the BR, including drugs not to be used with ritonavir (refer to prescribing information for drugs used as part of the BR); examples include the following: (Administration of any of the following medications must be discontinued at least 30 days prior to the Baseline/Day 1 visit and for the duration of the study)

Drug Class	**Agents Disallowed**
Alpha Adrenergic Receptor Antagonists	Alfuzosin
Antiarrythmics	Amiodarone, Flecainide Quinidine, Propafenone Systemic Lidocaine Mexilitine, Disopyramide
Antibacterials	Telithromycin
Anticonvulsants	Phenobarbital, Phenytoin, Carbamazepine
Antifungals	Voriconazole
Antihistamines	Astemizole, Terfenadine
Antimycobacterials	Rifampin, Rifabutin, Rifapentine
Calcium Channel Blockers	Felodipine, Bepridil, Nifedipine, Nicardipine, Verapamil, Diltiazem
Ergot Derivatives	Ergotamine, Ergonovine Dihydroergotamine Methylergonovine Ergometrine
GI Motility Agents	Cisapride
Herbal Supplements	St. John's Wort, Echinaccea
HMG-CoA Reductase Inhibitors	Simvastatin, Lovastatin, Cerivastatin
Immunosuppressants	Cyclosporine, Rapamycin, Sirolimus, Tacrolimus
Immunomodulators	Interleukin-2
Neuroleptics	Pimozide
Sedatives/Hypnotics	Midazolam, Triazolam
Systemic Chemotherapeutic (antineoplastic) Agents	All agents

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding and Treatment Codes

This is an open label study. Randomization, blinding and treatment codes are not applicable.

Elvitegravir will be provided by Gilead; subjects will be responsible to obtain and take their prescribed BR during the study.

Once eligibility is confirmed, the study site will complete an **Eligibility Worksheet** for each screened subject and submit for Sponsor review. The Sponsor will assign a unique subject number for each eligible subject and provide the subject number information to the study site.

The subject number assignment may be performed up to 7 days prior to the in-clinic baseline 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.

All baseline tests and procedures must be completed and eligibility confirmed prior to the administration of the first dose of study drug.

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

5.2. Description and Handling of Elvitegravir

5.2.1. Formulation

5.2.1.1. Elvitegravir Tablets – 50 mg, 85 mg, and 150 mg

Elvitegravir tablets are available in three strengths. Elvitegravir 50 mg, are light-green, round, film-coated tablets containing 50 mg of elvitegravir. Elvitegravir 85 mg, are light-green pentagon-shaped, film-coated tablets containing 85 mg of elvitegravir. Elvitegravir 150 mg, are light green triangle-shaped, film-coated tablets containing 150 mg of elvitegravir. Elvitegravir tablet cores contain croscarmellose sodium, hydroxypropyl cellulose, lactose monohydrate, microcrystalline cellulose, sodium lauryl sulfate, and magnesium stearate as inactive ingredients and are film-coated with polyvinyl alcohol, polyethylene glycol 3350, titanium dioxide, talc, FD&C Blue #2 aluminum lake, and iron oxide yellow. The 85 mg and 150 mg tablets are debossed with “GSI” on one side of the tablet and “85” and “150”, respectively, on the other side of the tablet. The 50 mg tablets are plain faced on both sides.

5.2.1.2. Elvitegravir Powder for Oral Suspension – 5 mg/mL

Elvitegravir powder for oral suspension is an off-white powder blend for constitution with 112 mL of water to prepare a suspension containing 5 mg/mL of elvitegravir. The powder blend contains microcrystalline cellulose, xanthan gum, xylitol, povidone, polysorbate, sodium benzoate, citric acid, and silicon dioxide. Each bottle contains approximately 6 grams of powder blend. GSI will be providing 10, 20, and 30 mL oral dosing syringes and bottle adapter for the elvitegravir suspension formula and be used as appropriate based on the suspension dosing volume.

5.2.2. Packaging and Labeling

Thirty (30) elvitegravir tablets (50 mg, 85 mg or 150 mg) are packaged in white high density polyethylene (HDPE) bottles with polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant screw cap with an induction-sealed, aluminum-faced liner.

Six (6) grams of elvitegravir powder blend for oral suspension are packaged in a natural, high density polyethylene (HDPE) bottle. Each bottle is enclosed with a white, continuous thread, child-resistant screw cap with an induction-sealed, aluminum-faced liner.

All labels for study drug bottles will meet all applicable requirements of the US Food and Drug Administration (FDA) and Annex 13 of EU Rules on Good Manufacturing Practices: Manufacture of investigational medicinal products (July 2010) and/or other local regulations as applicable.

5.2.3. Storage and Handling

Elvitegravir tablets should be stored at 25 °C (77 °F); excursions are permitted between 15 °C and 30 °C (59 °F and 86 °F, respectively). Storage conditions for the drug product are specified on the label. To ensure the stability of EVG tablets, it is recommended that the drug product not be dispensed into a container other than the container in which it is supplied.

Elvitegravir powder for oral suspension and EVG oral suspension following reconstitution should be stored at 25 °C (77 °F); excursions are permitted between 15 °C and 30 °C (59 °F and 86 °F, respectively). Exposure of this product to high humidity outside the original container for longer than two weeks is not recommended.

5.3. Dosage and Administration of Elvitegravir

Elvitegravir tablets and powder for oral suspension will be provided by Gilead Sciences and will be administered orally, once daily with food at approximately the same time each day. Dosage and administration of EVG is outlined below and in Table 5-1, Table 5-2, Table 5-3, and Table 5-4.

For subjects weighing ≥ 17 kg and receiving darunavir/r, tipranavir/r or fosamprenavir/r, the EVG dose will be as follows:

Table 5-1. EVG dose by Weight Range with DRV, fAPV or TPV

Weight range	EVG tablet dose w DRV, fAPV or TPV	EVG suspension dose w DRV, fAPV or TPV	mg/kg
≥34 kg	150 mg	30 mL	<4.4
≥28 to <34 kg	100 mg (2 x 50 mg tablets)	20 mL	2.9-3.6
≥17 to <28 kg	85 mg	17 mL	3.0-5.0

Note: For subjects who are not able to swallow tablets, EVG powder for oral suspension formulation (5 mg/mL) may be administered to obtain EVG doses of 50 mg, 85 mg, 100 mg, or 150 mg.

For subjects weighing ≥ 17 kg and receiving atazanavir/r or lopinavir/r, the EVG dose will be as follows:

Table 5-2. EVG dose by Weight Range with ATV, LPV

Weight range	EVG tablet dose w ATV, LPV	EVG suspension dose w ATV, LPV	mg/kg
≥30 kg	85 mg	17 mL	<2.8
≥17 to <30 kg	50 mg	10 mL	1.7-2.8

Note: For subjects who are not able to swallow tablets, EVG powder for oral suspension formulation (5 mg/mL) may be administered to obtain EVG doses of 50 mg, 85 mg, 100 mg, or 150 mg.

For subjects weighing < 17 kg and receiving darunavir/r, tipranavir/r or fosamprenavir/r, the EVG dose will be 4 mg/kg, using the EVG powder for oral suspension formulation (5 mg/mL) administered as an oral suspension. The EVG dose will be calculated based on subject's actual weight to provide 4 mg/kg, as follows:

Table 5-3. EVG Suspension dose (mL) by Body Weight with DRV, fAPV or TPV

Weight range	EVG suspension dose w DRV, fAPV or TPV
16 to <17 kg	13 mL
15 to <16 kg	12 mL
14 to <15 kg	12 mL
13 to <14 kg	11 mL
12 to <13 kg	10 mL
11 to <12 kg	9 mL
10 to <11 kg	8 mL
9 to <10kg	8 mL
8 to <9 kg	7 mL
7 to <8 kg	6 mL
6 to <7 kg	5 mL
5 to <6 kg	4 mL

For subjects weighing < 17 kg and receiving lopinavir/r or atazanavir/r, the EVG dose will be 2.4 mg/kg, using the EVG powder for oral suspension formulation (5 mg/mL) administered as an oral suspension. The EVG dose will be calculated based on subject's actual weight to provide 2.4 mg/kg, as follows:

Table 5-4. EVG Suspension dose (mL) by Body Weight with ATV, LPV

Weight range	EVG suspension dose w ATV, LPV
16 to <17 kg	8 mL
15 to <16 kg	7.5 mL
14 to <15 kg	7 mL
13 to <14 kg	6.5 mL
12 to <13 kg	6 mL
11 to <12 kg	5.5 mL
10 to <11 kg	5 mL
9 to <10kg	4.5 mL
8 to <9 kg	4 mL
7 to <8 kg	3.5 mL
6 to <7 kg	3 mL
5 to <6 kg	2.5 mL

In-clinic dosing will be performed at Baseline/Day 1, Weeks 16 and 40.

Subjects in Part A will also be administered their dose of study medication in the clinic with food during the Day 10 intensive PK visit. In order to allow for ease of PK sampling over a 10-hour period, subjects should be instructed to take their dose of elvitegravir together with food at the same time every day **in the morning (breakfast)**, during the 9 days leading up to intensive PK assessments. Prior to the scheduled PK visit subjects should fast overnight (a minimum of 8 hours), except for subjects in Part A Cohort 4. Microsampling of intensive PK timepoints will be implemented for subjects in Cohort 4.

After Week 48, all subjects receiving EVG who complete 48 weeks of study treatment will be given the option to participate in an extension phase of the study where Gilead will provide EVG until: a) the subject turns 18 and EVG is available for use in adults in the country in which the subject is enrolled or b) the age appropriate EVG formulation becomes available for use in the country in which the subject is enrolled or c) Gilead Sciences elects to terminate development of EVG in the applicable country.

Subjects and parents/guardians will be instructed to bring all study medication in the original container at each study visit for drug accountability (unless otherwise specified in Section 6). Refer to Section 5.5 for information on the Investigator's responsibilities of IMP.

5.3.1. Elvitegravir Powder for Oral Suspension Reconstitution and Dosing

Reconstitution Instructions:

Elvitegravir powder for oral suspension must be reconstituted by the study pharmacist prior to dispensation to subjects' parent/guardian.

1. Tap the closed bottle several times to loosen the powder.
2. Measure 112 mL of water in a graduated cylinder.
3. Unscrew the child-resistant cap from the bottle.
4. Remove and discard the aluminum seal.
5. Add half of the water (~60 mL) and shake the closed bottle well for about 15 to 30 seconds.
6. Add the rest of the water and shake vigorously for 15 seconds to obtain a uniform suspension.
7. Remove the child-resistant cap and push the bottle adapter into the neck of the bottle.
8. Tightly close the bottle with the child-resistant cap. This will assure proper seating of the bottle adapter in the bottle and child-resistant status of the cap.
9. Apply a label on the bottle stating the preparation date and an end-of-use date of **no more than 30 days** beyond the preparation date (e.g., compounding date).
10. Apply "Shake Well Before Use" labels on the bottle. After constitution the bottle will contain approximately 120 mL of a suspension of 5 mg/mL elvitegravir suspension.

Dosing Instructions:

11. The provided graduated 10, 20, or 30 mL oral dosing syringe will be used to measure the appropriate dose volume of elvitegravir oral suspension to the subject. Refer to Table 5-1, Table 5-2, Table 5-3, and Table 5-4 for detailed dosage information.
12. Insert the syringe into the adapter.
13. With the syringe, adapter and bottle attached, turn the entire assembly upside down.
14. Pull the plunger to withdraw the suspension sample for use.

15. Administer study drug directly to subject's mouth via the syringe.

5.4. Prior and Concomitant Medications

Subjects receiving oral contraceptives or patch contraceptives should consider other methods of contraception as concentrations of ethinyl estradiol, norgestimate or norethindrone may increase or decrease on coadministration with study drug. Please refer to Section 7.7.2 for guidance on the use of contraception methods.

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

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

Medications listed in the following table and use of herbal/natural supplements are excluded or should be used with caution while subjects are participating in the study:

Drug Class	Agents Disallowed	Use Discouraged and To Be Used With Caution
Alpha Adrenergic Receptor Antagonist	Alfuzosin	
Antacids		Subjects may not take antacids (e.g., Tums or Rolaids); the ulcer medication sucralfate (Carafate); or vitamin or mineral supplements that contain calcium, iron or zinc for a minimum of 2 hours before and 2 hours after any dose of elvitegravir/r.
Antiarrythmics	Amiodarone, Flecainide Quinidine, Propafenone Systemic Lidocaine Mexilitine, Disopyramide	
Antibacterials	Telithromycin	
Anticoagulants		Warfarin: Frequent INR (International Normalized Ratio) monitoring upon initiation of ritonavir-boosted elvitegravir treatment is recommended.
Anticonvulsants	Phenobarbital, Phenytoin, Carbamazepine	

Drug Class	Agents Disallowed	Use Discouraged and To Be Used With Caution
Antifungals	Voriconazole	Ketoconazole and Itraconazole: concomitant use with study drug may also result in an increase or decrease in concentrations. Subjects receiving antifungals should be monitored for adequate clinical response. Daily dose of ketoconazole and itraconazole should be restricted to 200mg.
Antigout		Colchicine is a P-gp and CYP3A4 substrate. Concentrations may increase with study drug. Dose reductions of colchicine may be required. Should not be coadministered in patients with renal or hepatic impairment. Treatment of gout – Colchicine is not indicated for treatment of gout in pediatric populations. Treatment of familial Mediterranean fever – coadministration of colchicine in patients receiving EVG/r: Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day).
Antihistamines	Astemizole, Terfenadine	
Antimycobacterials	Rifampin, Rifabutin, Rifapentine	
Antiretroviral Agents	Any drug with antiretroviral activity not allowed as part of the prescribed BR	
Calcium Channel Blockers	Felodipine, Bepridil, Nifedipine, Nicardipine, Verapamil, Diltiazem	
Endothelin Receptor Antagonists		Bosentan: Coadministration may lead to decreased elvitegravir exposures and loss of therapeutic effect and development of resistance. Alternative endothelin receptor antagonists may be considered.
Ergot Derivatives	Ergotamine, Ergonovine Dihydroergotamine Methylergonovine Ergometrine	

Drug Class	Agents Disallowed	Use Discouraged and To Be Used With Caution
GI Motility Agents	Cisapride	
Herbal Supplements	St. John's Wort, Echinaccea	
HMG-CoA Reductase Inhibitors	Simvastatin, Lovastatin, Cerivastatin	Atorvastatin, Rosuvastatin, Pravastatin: Start with lowest possible dose with careful monitoring for signs and symptoms of muscle weakness or myopathy, including rhabdomyolysis. Gradual increase in dose may be tailored to clinical response.
Immunosuppressants	Cyclosporine, Rapamycin, Sirolimus, Tacrolimus	
Immunomodulators	Interleukin-2	
Neuroleptics	Pimozide	
Opiates		Methadone: Monitoring for signs and symptoms of methadone withdrawal is recommended. Some subjects may require a modification of their methadone dose. Meperidine (Pethidine): Dosage increase and long-term use are not recommended due to increased levels of metabolite normeperidine, which has analgesic and CNS stimulant (e.g., seizures) activities. Buprenorphine: As a substrate of CYP3A4, concomitant use of this agent with study treatments may result in higher or lower systemic exposure. Careful monitoring for signs and symptoms of respiratory and CNS depression, and for opiate withdrawal is recommended.
Phosphodiesterase-5 Inhibitors		Sildenafil, Vardenafil, Taladafil: It is recommended that a single dose of Sildenafil no more than 25 mg in 48 hours, Vardenafil no more than 2.5 mg in 72 hours, or Taladafil no more than 10 mg in 72 hours be coadministered with study treatments.
Sedatives/Hypnotics	Midazolam, Triazolam	

Drug Class	Agents Disallowed	Use Discouraged and To Be Used With Caution
Systemic Chemotherapeutic (antineoplastic) Agents	All agents	
Systemic Corticosteroids dexamethasone		Systemic dexamethasone, a CYP3A inducer, may significantly decrease elvitegravir plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Alternative corticosteroids should be considered.
Corticosteroids Inhaled/Nasal: fluticasone		Use of inhaled or oral corticosteroid and study drug may increase plasma concentrations of fluticasone and is not recommended unless the potential benefit to the subject outweighs the risks. Coadministration of fluticasone propionate and ritonavir is not recommended unless the potential benefit to the subject outweighs the risks of corticosteroid side effects. Alternative corticosteroids should be considered, particularly for long term use. Use of Prednisone as a steroid burst (≤1 week of use) should be monitored appropriately.

5.5. Accountability for Elvitegravir

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

EVG accountability records will be provided to each study site to:

- Record the date received and quantity of IMP bottles.
- Record the date, subject number, subject initials, the IMP bottle 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

If applicable, the monitor will evaluate the site's standard operating procedure for investigational medicinal product disposal/destruction in order to ensure that it complies with Gilead Sciences requirements. Drug may be returned or destroyed on an ongoing basis during the study if appropriate. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused investigational medicinal product supplies, including empty containers, according to these procedures. If the site cannot meet Gilead Sciences requirements for disposal, arrangements will be made between the site and Gilead Sciences or its representative for destruction or return of unused investigational medicinal product supplies. Refer to Section 9.1.7 for more details.

6. STUDY PROCEDURES

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

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

6.1. Subject Enrollment and Treatment Assignment

It is the responsibility of the investigator to ensure that each subject is eligible for the study before enrollment.

Please refer to Section 5.1 for details about subject number assignment.

6.2. Pretreatment Assessments

6.2.1. Screening Visit

Each subject who has the ability to read and write must sign an assent (and parent or legal guardian sign an informed consent form) prior to the conduct of any screening procedures. Subjects will be assigned a screening number at the time of assent/consent. Screening evaluations are used to determine the eligibility of each candidate for study enrollment.

The following will be performed and documented at screening:

6.2.1.1. Obtain written assent/consent

6.2.1.2. Obtain medical and medication history including history of HIV-1 disease-related events and any other ongoing medications within 30 days of the screening visit. **For Cohorts 3 and 4 only**, obtain maternal medical history for HBV and HCV.

6.2.1.3. Perform a complete physical examination including, vital signs, body weight, and height/length (urogenital/anorectal exams will be performed at the discretion of the investigator).

6.2.1.4. Obtain urine samples for urinalysis

6.2.1.5. Obtain blood samples for the following laboratory analyses:

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

- Chemistry profile: Albumin, alkaline phosphatase, AST, ALT, direct bilirubin, total bilirubin, bicarbonate, BUN, calcium, chloride, CPK, creatinine, magnesium, phosphorus, potassium, total protein, sodium, uric acid, amylase and lipase

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

- Estimated glomerular filtration rate (eGFR) using the Schwartz Formula: eGFR (mL/min/1.73m2) = k × L/Scr (k is a proportionality constant, refer to Section 4.2 for details); L is height in centimeters (cm); and S_{cr} is serum creatinine (mg/dL)]

- Plasma HIV-1 RNA

- CD4+ cell count and percentage

- HBV surface antigen serology (HBsAg screening), **except for Cohorts 3 and 4** (see 6.2.1.2).

- HCV antibody serology (HCVAb screening), **except for Cohorts 3 and 4** (see 6.2.1.2).

- HIV-1 integrase, reverse transcriptase and protease genotype (only if screening HIV-1 RNA is >1,000 copies/mL). The HIV-1 genotype may not be performed for subjects that fail to meet other screening laboratory criteria. For subjects with HIV-1 RNA <50 copies/mL at screening, historical genotypes should be provided, if available.

6.2.1.6. Obtain 12-lead ECG, performed supine

6.2.1.7. Record any adverse events occurring after signing of the consent form.

From the time of obtaining informed consent through the first administration of IMP, record all serious adverse events (SAEs), as well as any non-serious adverse events related to protocol-mandated procedures on the adverse events case report form (CRF/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 CRF/eCRF. See Section 7 for additional details.

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 35 days after the screening visit for the Baseline/Day 1 assessments. The screening window may be extended to 42 days for subjects who require repeat testing of the HIV-1 genotype or if the screening visit is divided into multiple visits.

Subjects with exclusionary screening laboratory results due to an acute clinical condition which resolves can be re-screened within 3 months of initial screening. The decision to re-screen the subject will be made in consultation with the Medical Monitor, and written notice of eligibility from the Sponsor is required before a re-screened subject can be enrolled.

Complete the Eligibility Worksheet for each screened subject and submit to Sponsor for review prior to assignment of subject number. The subject number assignment may be performed up to 7 days prior to the in-clinic baseline visit provided that all other screening procedures have been completed and subject eligibility has been confirmed.

6.2.2. Baseline Assessments

The following evaluations are to be completed at the Baseline/Day 1 visit. The subject must complete all study procedures before being administered the study drug:

6.2.2.1. Perform a complete physical examination including, vital signs, body weight, and height/length.

6.2.2.2. Perform Tanner Stage assessment (Appendix 6) for subjects ≥ 6 years of age at the time of the visit, until Tanner Stage 5 has been reached. Date of first menses will be documented.

6.2.2.3. Obtain urine samples for the following procedures:

- Urinalysis
- Urine pregnancy test (females of childbearing potential only). If the urine pregnancy test is positive at baseline, 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 in the study.
- Urine sample storage for possible additional testing

6.2.2.4. Obtain blood samples for the following laboratory analyses:

- Chemistry profile: Albumin, alkaline phosphatase, AST, ALT, direct bilirubin, total bilirubin, bicarbonate, BUN, calcium, chloride, CPK, creatinine, magnesium, phosphorus, potassium, total protein, sodium, uric acid, amylase and lipase
- Hematology profile: CBC with differential and platelet count

- Metabolic assessments: fasting glucose and lipid panel (total cholesterol, HDL, direct LDL, triglycerides) evaluated for subjects failing a current antiretroviral regimen (HIV-1 RNA >1,000 copies/mL) only and weighing at ≥ 13 kg at the time of the visit. 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 for a re-draw of the metabolic assessments. **For Cohorts 2 and 3 only,** direct LDL will be calculated if subjects weigh <15.8 kg at the time of the visit.
- eGFR using the Schwartz Formula (refer to Section 4.2 for details)
- Plasma HIV-1 RNA
- CD4+ cell count and percentage
- **For Cohorts 1 and 2 only**: plasma storage sample for possible additional testing

6.2.2.5. Review of AEs and concomitant medication

6.2.2.6. Study drug dispensation: study drug will be dispensed in an open-label fashion

6.2.2.7. Upon completion of the Baseline/Day 1 assessments and procedures, the subject will be administered the first dose of EVG + PI/r and other BR components per dosing requirements. Review dosing instructions with subject and/or parent/guardian.

6.2.2.8. Assess palatability of EVG suspension formulation, as applicable

6.2.2.9. **For Part A subjects only**: provide subject diary cards

The Part A intensive PK evaluation is designed to assess the PK and confirm the dose of EVG in pediatric subjects. Therefore, all subjects must take their QD dose of EVG + PI/r and other BR components with food in the morning through Day 9 at approximately the same time every day.

6.3. Treatment Assessments

6.3.1. Week 1 (Day 7) and Week 3 Telephone Visits

The Week 1 (Day 7) and Week 3 visits should occur within ± 2 days of the protocol-specified visit date based on the Baseline/Day 1 visit.

The following evaluations will be reviewed over the telephone with the subject and/or parent/guardian:

6.3.1.1. Review treatment adherence with subject and/or parent/guardian.

6.3.1.2. Review of AEs and concomitant medications.

6.3.1.3. **For the Week 1 visit and Part A only:**

- Review subject diary cards
- Remind subject and/or parent/guardian to come in for the Day 10 intensive PK visit **without taking** their dose of the EVG + PI/r and other BR components
- Remind subject and/or parent/guardian to come in a fasted state for the Day 10 intensive PK visit (ie**, no food or drink except water at least 8 hours prior to the Day 10 intensive PK visit)**. **Note:** fasting is not required for subjects in Part A Cohort 4.
- Remind subject and/or parent/guardian to bring the drug bottles of the EVG + PI/r and other BR components with them for in-clinic dosing and drug accountability at the Day 10 intensive PK visit.
- Remind subject and/or parent/guardian to bring the completed diary cards to the Day 10 intensive PK visit.

6.3.2. Day 10 Intensive PK Visit – Part A only

The Day 10 intensive PK visit should occur on the protocol-specified visit date based on the Baseline/Day 1 visit. For the purposes of scheduling, the Day 10 intensive PK visit may be performed within + 4 days of the protocol-specified visit date.

Subjects should come in a fasted state for the Day 10 intensive PK visit (ie, no food or drink except water at least 8 hours prior to the Day 10 intensive PK visit). Subjects and/or parents/guardians should be instructed that the Day 10 dose of EVG + PI/r and other BR components must **not** be taken until the evaluations listed below are completed. **Note:** fasting is not required for subjects in Cohort 4.

If the subject has already dosed prior to the Day 10 clinic visit or is **not** in a fasted state, the Day 10 intensive PK assessments must not be completed. The subject and/or parents/guardians should be instructed to return in a fasted state within 4 days (Days 11, 12, 13, or 14) for the intensive PK visit. Appropriate study drug re-dispensation must be performed in this case.

If dosing non-compliance not related to AEs is identified on or prior to the Day 10 visit, the Day 10 intensive PK assessments must not be completed. The subject and/or parents/guardians should be counseled regarding proper dosing and be scheduled to return

for the Day 10 intensive PK visit no sooner than 3 days following compliant dosing and no later than Day 14 (ie, return on Day 13 or Day 14).

In both scenarios described above, the subject and/or parents/guardians should be reminded not to take the EVG + PI/r and other BR components prior to arriving at the clinic on the day of the re-scheduled intensive PK visit. All Day 10 intensive PK assessments listed below should be completed when the subject returns.

If dosing non-compliance due to an AE is identified on or prior to the Day 10 visit, the Day 10 intensive PK assessments must not be completed. Consultation with the Gilead Medical Monitor is required regarding the potential of rescheduling the Day 10 intensive PK visit.

The following evaluations are to be completed at the Day 10 intensive PK visit:

6.3.2.1. Perform a symptom-directed physical examination as needed.

6.3.2.2. Obtain vital signs and body weight.

6.3.2.3. Obtain urine samples for the following procedures:

- Urinalysis
- Urine pregnancy test (females of childbearing potential only). If the urine pregnancy test is positive, EVG therapy will be suspended and intensive PK sampling will not be completed. The positive result will be confirmed with a serum pregnancy test. If the serum pregnancy test is positive, EVG therapy will be discontinued. If pregnancy is not confirmed, consultation with the Gilead Medical Monitor is required regarding the potential of resuming EVG therapy and completing intensive PK sampling.
- Urine sample storage for possible additional testing

6.3.2.4. Obtain blood samples for the following laboratory analyses:

- Chemistry profile: Albumin, alkaline phosphatase, AST, ALT, direct bilirubin, total bilirubin, bicarbonate, BUN, calcium, chloride, CPK, creatinine, magnesium, phosphorus, potassium, total protein, sodium, uric acid, amylase and lipase
- Hematology profile: CBC with differential and platelet count
- eGFR using the Schwartz Formula (refer to Section 4.2 for details)
- Plasma HIV-1 RNA

6.3.2.5. Perform intensive PK sampling:

- Blood samples will be collected at 0 (predose, ≤ 30 minutes prior to dosing). After collection of the predose sample, subjects will be provided a standardized meal. **Within 5 minutes after consuming the standardized meal**, subjects will be dosed with their EVG + PI/r and other BR components per dosing requirements.
- Postdose blood samples will be collected as follows:
  - For Cohorts 2 and 3: at 1.5, 2.5, 3.5, 5, 8, 10, and 12 hours postdose.
  - For Cohort 4: at 3, 3.5, 5, and 8 hours postdose.
- Subjects will be restricted from food intake until after the 4 hours after dosing, **except for subjects in Cohort 4**. Please also refer to the PK manual for details about standardized meals and PK sample processing instructions.

6.3.2.6. Assess palatability of EVG suspension formulation, as applicable

6.3.2.7. Review and collect subject diary cards

6.3.2.8. Perform study drug accountability (**Note:** study drug will not be dispensed at this visit).

6.3.2.9. Review treatment adherence with subject and/or parent/guardian.

6.3.2.10. Review of AEs and concomitant medications

After completing the Day 10 intensive PK visit:

- Subjects with HIV-1 RNA <50 copies/mL at screening will **discontinue** EVG and return to the clinic for a 30-Day follow-up visit (refer to Section 6.3.1).
- Subjects with HIV-RNA >1,000 copies/mL at screening will continue taking study drug and study visits through Week 48 as described in Section 6.3.3.

6.3.3. Week 4 – 48 Visits

Subjects failing a current antiretroviral regimen (HIV-1 RNA >1,000 copies/mL at screening) will continue taking their study drugs through Week 48. It is recommended that all subjects take their dose of EVG + PI/r and other BR components along with food at approximately the same time each day (with the exception of in-clinic dosing at Weeks 16 and 40 visits).

The Week 4 visit is to be completed 31 to 33 days from the Baseline visit. The other study visits are to be completed within ± 2 days of the protocol-specified visit date based on the Baseline visit for Week 8 and completed within ± 4 days of the protocol-specified visit date thereafter through Week 48 unless otherwise specified. **Regularly scheduled evaluations will be completed on all subjects whether or not they continue to receive study drug**.

The following evaluations are to be completed at Weeks 4, 8, 12, 16, 24, 32, 40, and 48 unless otherwise specified:

6.3.3.1. Perform a complete physical examination (**Weeks 24 and 48**) or a symptom-directed physical examination as needed

6.3.3.2. Obtain vital signs and body weight

6.3.3.3. Obtain height/length. For subjects ≥ 1 year of age, obtain measurements at **Weeks 12, 24, and 48 only.** For subjects < 1 year of age, obtain measurements at all visits.

6.3.3.4. Perform Tanner Stage assessments (Appendix 6) for subjects ≥ 6 years of age at the time of the visit, at **Weeks 24 and 48**, until Tanner Stage 5 has been reached. Date of first menses will be documented.

6.3.3.5. Obtain urine samples for the following procedures:

- Urinalysis (**Weeks 4, 12, 24, and 48 only**)
- Urine sample storage for possible additional testing (**Weeks 4, 12, 24, and 48 only**)
- Urine pregnancy test (females of childbearing potential only). If the urine pregnancy test is positive, 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 continue in the study. (**all visits**)

6.3.3.6. Obtain blood samples for the following laboratory analyses:

- Chemistry profile: Albumin, alkaline phosphatase, AST, ALT, direct bilirubin, total bilirubin, bicarbonate, BUN, calcium, chloride, CPK, creatinine, magnesium, phosphorus, potassium, total protein, sodium, uric acid, amylase and lipase
- Hematology profile: CBC with differential and platelet count

- Metabolic assessments: fasting glucose and lipid panel (total cholesterol, HDL, direct LDL, triglycerides) evaluated for all subjects weighing at ≥ 13 kg at the time of the visit (**Weeks 24 and 48**). The subject and/or parents/guardians should be reminded to fast prior to the Week 24 and 48 visits. If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state for a re-draw of the metabolic assessments. **For Cohorts 2 and 3 only,** direct LDL will be calculated if subjects weigh <15.8 kg at the time of the visit.
- eGFR using the Schwartz Formula (refer to Section 4.2 for details)
- Plasma HIV-1 RNA
- CD4+ cell count and percentage
- Trough (20 to 24 hours postdose) plasma PK sample at **Weeks 16 and 40**
- Random single plasma PK sample for descriptive PK at **Weeks 4, 8, 12, and 32. For Week 12, obtain sample for Cohorts 1, 2, and 4 only.**
- Plasma storage sample for possible additional testing at **Weeks 12, 24 and 48 for Cohorts 1, 2 and 3 only.**

6.3.3.7. Subjects who meet the criteria for Suboptimal Virologic Response will be managed according to the Suboptimal Virologic Response Schema (Section 6.8.1)

6.3.3.8. Subjects who meet the criteria for Virologic Rebound will be managed according to the Virologic Rebound Schema (Section 6.8.2)

6.3.3.9. **For Weeks 16 and 40 only:** upon completion of the above assessments and procedures, the subject will be administered their dose of the EVG + PI/r and other BR components along with food

6.3.3.10. Assess palatability of EVG suspension formulation at **Weeks 24 and 48**, as applicable

6.3.3.11. Perform study drug accountability and dispensation.

6.3.3.12. Review treatment adherence with subject and/or parent/guardian.

6.3.3.13. Review of AEs and concomitant medications

6.4. Post Week 48 Assessments

Study subjects receiving EVG who complete 48 weeks of study treatment will be given the option to participate in an extension phase of the study where Gilead will provide EVG until: a) the subject turns 18 and EVG is available for use in adults in the country in which the subject is enrolled or b) EVG becomes available for use in children or adolescents in the country in which the subject is enrolled or c) Gilead Sciences elects to terminate development of EVG in the applicable country. Subjects who are eligible to participate in the study extension must demonstrate evidence of response to EVG or show absence of resistance to EVG for subjects with HIV-1 RNA > 400 copies/mL at Week 48.

Subjects who choose to receive EVG will return for study visits every 12 weeks. Study visits are to be completed within ± 6 days of the protocol-specified visit date unless otherwise specified.

6.4.1.1. Perform a symptom-directed physical examination as needed

6.4.1.2. Obtain vital signs, body weight, and height/length.

6.4.1.3. Perform Tanner Stage assessments (Appendix 6) for subjects ≥ 6 years of age at the time of the visit, **every 48 weeks**, until Tanner Stage 5 has been reached. Date of first menses will be documented.

6.4.1.4. Obtain urine samples for the following procedures:

- Urinalysis
- Urine pregnancy test (females of childbearing potential only). If the urine pregnancy test is positive, 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 continue in the study.
- Urine sample storage for possible additional testing

6.4.1.5. Obtain blood samples for the following laboratory analyses:

- Chemistry profile: Albumin, alkaline phosphatase, AST, ALT, direct bilirubin, total bilirubin, bicarbonate, BUN, calcium, chloride, CPK, creatinine, magnesium, phosphorus, potassium, total protein, sodium, uric acid, amylase and lipase
- Hematology profile: CBC with differential and platelet count

- Metabolic assessments: fasting glucose and lipid panel (total cholesterol, HDL, direct LDL, triglycerides) evaluated for all subjects weighing at ≥ 13 kg at the time of the visit (**every 48 weeks**). The subject and/or parents/guardians should be reminded to fast prior to the visits. If the subject has not fasted prior to the visit, the visit may proceed, but the subject must return within 72 hours in a fasted state for a re-draw of the metabolic assessments. **For Cohorts 2 and 3 only,** direct LDL will be calculated if subjects weigh <15.8 kg at the time of the visit.
- eGFR using the Schwartz Formula (refer to Section 4.2 for details)
- Plasma HIV-1 RNA
- CD4+ cell count and percentage
- Random single plasma PK sample for descriptive PK
- Plasma storage sample for possible additional testing

6.4.1.6. Subjects who meet the criteria for Virologic Rebound will be managed according to the Virologic Rebound Schema (Section 6.8.2)

6.4.1.7. Perform study drug accountability and dispensation.

6.4.1.8. Review treatment adherence with subject and/or parent/guardian.

6.4.1.9. Review of AEs and concomitant medications.

6.5. Assessments for Premature Discontinuation from Study

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 6.3). If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

6.5.1. Early Study Drugs Discontinuation (ESDD)

If a Part A subject discontinues study drug prior to Day 10, the subject will be asked to return to the clinic within 72 hours of stopping study drug for an ESDD visit.

Subjects with HIV-1 RNA >1,000 copies/mL at screening (failing a current antiretroviral regimen) and who discontinue study drugs any time prior to Week 48 will be asked to return to the clinic within 72 hours of stopping study drugs for an ESDD visit. Subjects will then be asked to continue attending all scheduled study visits.

At the ESDD visit, any evaluations showing abnormal results for which there is a reasonable possibility of a 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 ESDD visit:

6.5.1.1. Perform a complete physical examination including vital signs, body weight, and height/length.

6.5.1.2. Obtain urine samples for the following procedures:

- Urinalysis
- Urine pregnancy test (females of childbearing potential only). If the urine pregnancy test is positive, the result will be confirmed with a serum pregnancy test.
- Urine sample storage for possible additional testing

6.5.1.3. Obtain blood samples for the following laboratory analyses:

- Chemistry profile: Albumin, alkaline phosphatase, AST, ALT, direct bilirubin, total bilirubin, bicarbonate, BUN, calcium, chloride, CPK, creatinine, magnesium, phosphorus, potassium, total protein, sodium, uric acid, amylase and lipase
- Hematology profile: CBC with differential and platelet count
- eGFR using the Schwartz Formula (refer to Section 4.2 for details)
- Plasma HIV-1 RNA
- CD4+ cell count and percentage
- Plasma storage sample for possible additional testing

6.5.1.4. Obtain 12-lead ECG performed supine.

6.5.1.5. Perform study drug accountability.

6.5.1.6. Review of AEs and concomitant medications.

6.6. 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
- Therapeutic failure (ie, virologic failure, see Section 6.8 for details)
- Subject request to discontinue for any reason
- Subject noncompliance
- Pregnancy during the study; refer to Section 7.8
- Discontinuation of the study at the request of Gilead, a regulatory agency or an IRB/IEC

6.7. End of Study

For Part A subjects with suppressed viremia (HIV-1 RNA <50 copies/mL at screening), the end of study is defined as the completion of Day 10 and the 30-Day Follow-up visit.

For subjects failing a current antiretroviral regimen (HIV-1 RNA >1,000 copies/mL at screening), the end of study is defined as the completion of 48 weeks on study drug and the 30-Day Follow-up visit, or for subjects enrolled in the extension phase, when: a) the subject turns 18 and EVG is available for use in adults in the country in which the subject is enrolled or b) the age appropriate EVG formulation becomes available for use in the country in which the subject is enrolled or c) Gilead Sciences elects to terminate development of EVG in the applicable country.

6.7.1. 30-Day Follow-Up Assessments

Part A subjects with suppressed viremia (HIV-1 RNA <50 copies/mL at screening) who complete the Day 10 intensive PK visit will discontinue EVG after the Day 10 dose and will return to the clinic 30 days after completion of the Day 10 visit for a 30-Day Follow-up visit.

Subjects failing a current antiretroviral regimen /(HIV-1 RNA >1,000 copies/mL at screening) who complete 48 weeks on study drug will be required to return to the clinic 30 days after completion of the Week 48 visit for a 30-Day Follow-up visit only if they do not wish to enroll in the extension phase of the study.

Subjects who discontinue study drug and do not wish to continue in the study will be required to return to the clinic 30 days after completion of an ESDD visit for a 30-Day Follow-Up visit. Those subjects who permanently discontinue study drug and continue in the study through at least one subsequent visit after the ESDD visit will not be required to complete the 30-Day Follow-Up visit.

The following evaluations are to be completed at the 30-Day Follow-Up visit:

6.7.1.1. Perform a symptom-directed physical examination as needed

6.7.1.2. Obtain vital signs and body weight.

6.7.1.3. Obtain urine samples for the following procedures:

- Urinalysis
- Urine pregnancy test (females of childbearing potential only). If the urine pregnancy test is positive, the result will be confirmed with a serum pregnancy test.
- Urine sample storage for possible additional testing

6.7.1.4. Obtain blood samples for the following laboratory analyses:

- Chemistry profile: Albumin, alkaline phosphatase, AST, ALT, direct bilirubin, total bilirubin, bicarbonate, BUN, calcium, chloride, CPK, creatinine, magnesium, phosphorus, potassium, total protein, sodium, uric acid, amylase and lipase
- Hematology profile: CBC with differential and platelet count
- Plasma HIV-1 RNA
- CD4+ cell count and percentage

6.7.1.5. Review of AEs and concomitant medications.

At the 30-Day Follow-Up Visit, any evaluations showing abnormal results for **which 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.

6.8. Virologic Failure

Resistance testing will be performed in subjects who experience suboptimal virologic response, virologic rebound, and at Week 48 or last visit on study at or after Week 8 if HIV-1 RNA is ≥ 400 copies/mL. Subjects who experience either suboptimal virologic response or virologic rebound, as defined below (see Sections 6.8.1 and 6.8.2), will be considered to have virologic failure.

6.8.1. Management of Suboptimal Virologic Response

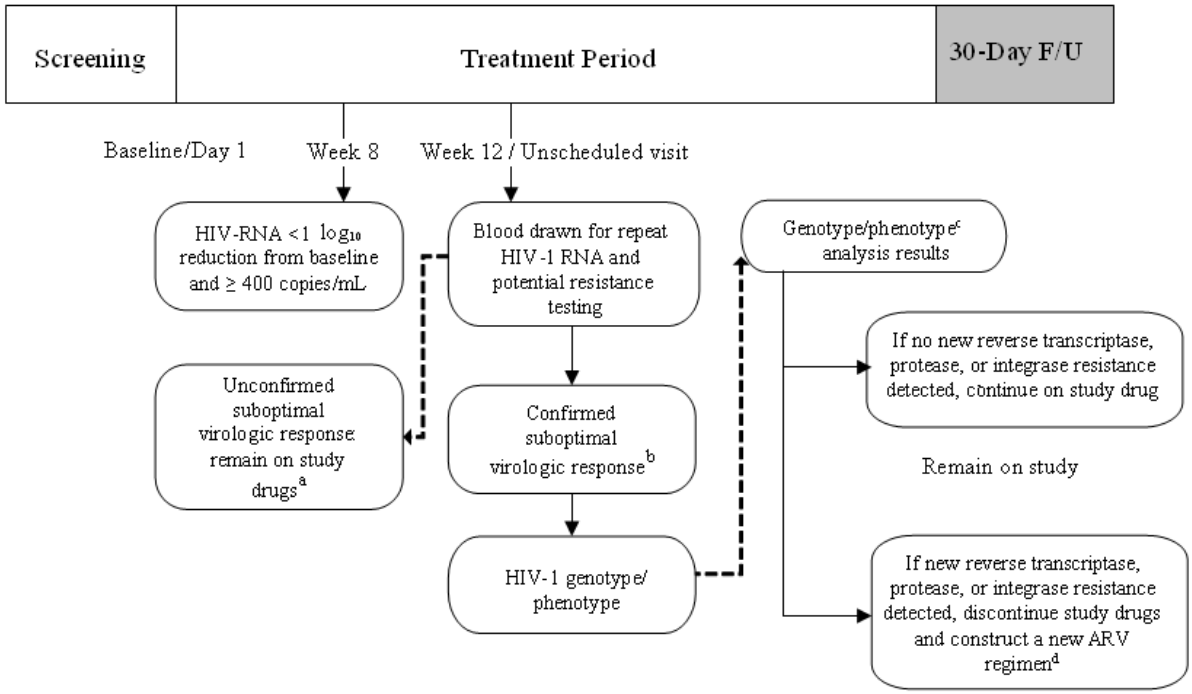
Subjects who meet the criteria listed below will be considered to have suboptimal virologic response:

- HIV-1 RNA < 1 $\log_{10}$ reduction from Baseline **and** ≥ 400 copies/mL at the Week 8 and confirmed at Week 12 or the next unscheduled visit at least 2 weeks after Week 8.

Following the unconfirmed suboptimal virologic response, HIV-1 RNA levels will be monitored at the next scheduled or unscheduled visit, and blood may be drawn for potential HIV-1 resistance testing (reverse transcriptase, protease, and integrase) (e.g., the Week 12 visit for those subjects flagged as having unconfirmed suboptimal virologic response at Week 8).

- Please refer to Figure 6-1 for the management of subjects who meet the criteria for Suboptimal Virologic Response.

Figure 6-1. Suboptimal Virologic Response Schema



a If suboptimal virologic response is not confirmed, the subject will remain on their assigned study drug.

b If suboptimal virologic response is confirmed, the HIV-1 resistance testing (reverse transcriptase, protease, and integrase) will be analyzed only if the HIV-1 RNA is ≥ 400 copies/mL.

c If the genotyping/phenotyping assay fails to provide results, an additional specimen will be sent for analysis and a new ARV regimen may be configured at the discretion of the Investigator, in consultation with the Medical Monitor.

d Based on the results of the genotype/phenotype assays, the subject's current regimen may be discontinued or altered (ie, remain on study drugs, remain on open-label elvitegravir and reconfigure BR, or switch to regimen without open-label elvitegravir) and the subject will remain in the study through Week 48.

6.8.2. Management of Virologic Rebound

Subjects who meet any one of the criteria listed below will be considered to be a potential virologic failure:

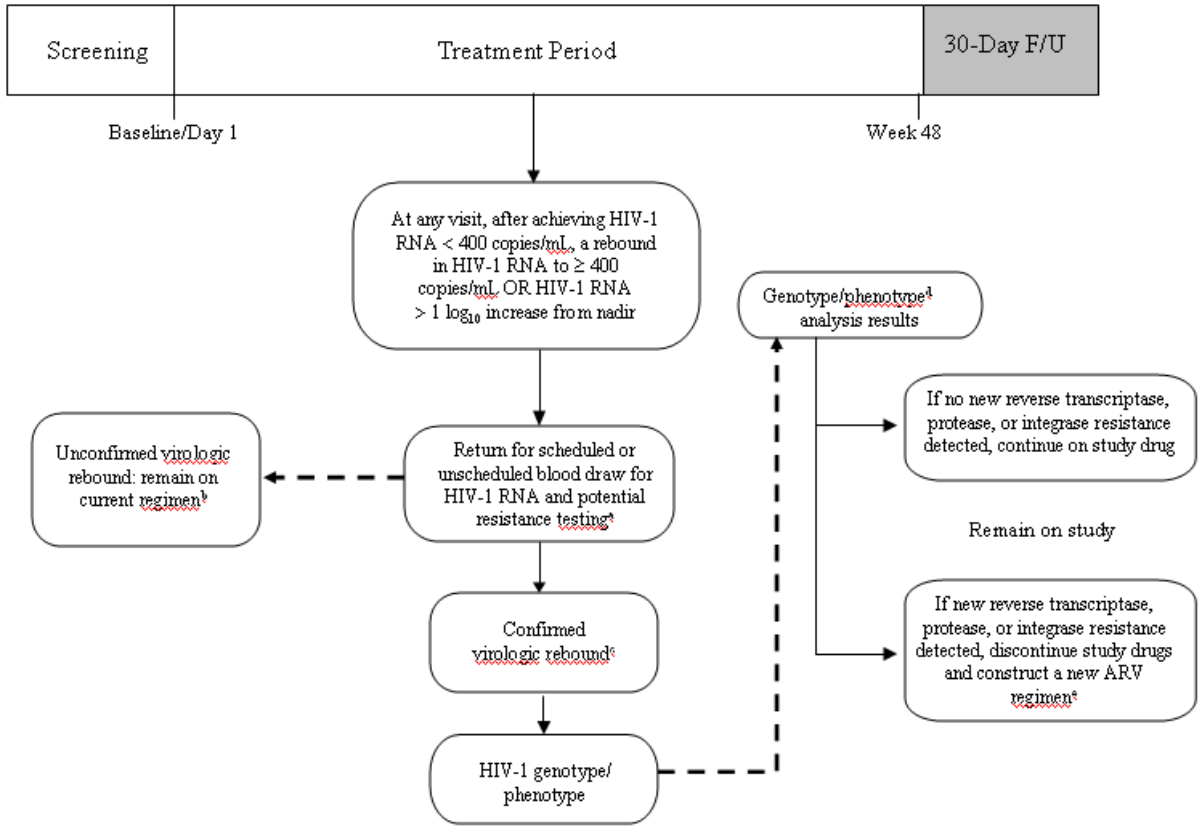
- At any visit, after achieving HIV-1 RNA < 400 copies/mL, a rebound in HIV-1 RNA to ≥ 400 copies/mL, which is subsequently confirmed at the following scheduled or unscheduled visit at least 2 weeks after date of original test with HIV-1 RNA ≥ 400 copies/mL

- At any visit, a > 1 $\log_{10}$ increase of HIV-1 RNA from nadir, which is subsequently confirmed at the following scheduled or unscheduled visit at least 2 weeks after date of original test with HIV-1 RNA > 1 $\log_{10}$ increase from nadir

Following the unconfirmed virologic rebound, subjects will be asked to return to the clinic for a scheduled or unscheduled HIV-1 RNA and HIV-1 resistance testing (reverse transcriptase, protease, and integrase) blood draw.

Please refer to Figure 6-2 for the management of subjects who meet the criteria for Virologic Rebound.

Figure 6-2. Virologic Rebound Schema



a At least 2 weeks after original elevated HIV-1 RNA test.

b If virologic rebound is not confirmed, the subject will remain on their assigned study drug.

c If virologic rebound is confirmed, HIV-1 resistance testing (reverse transcriptase, protease and integrase) will be analyzed only if the HIV-1 RNA is ≥ 400 copies/mL.

d If the genotyping/phenotyping assay fails to provide results, an additional specimen will be sent for analysis and a new ARV regimen may be configured at the discretion of the Investigator, in consultation with the Medical Monitor.

e Based on the results of the genotype/phenotype assays, the subject's current regimen may be discontinued or altered (ie, remain on study drugs, remain on open-label elvitegravir and reconfigure BR, or switch to regimen without open-label elvitegravir) and the subject will remain in the study through Week 48.

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 pharmaceutical 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 7.1.1and 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 subinvestigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship to IMP therapy using clinical judgment and the following considerations:

- **No**: Evidence exists that the adverse event has an etiology other than the IMP. 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 investigational medicinal product.

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

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

All SAEs, regardless of cause or relationship, that occur 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 CRF/eCRF database and Gilead Drug Safety and Public Health (DSPH) as instructed. This also includes any SAEs resulting from protocol-associated procedures performed from screening onwards.

All AEs, regardless of cause or relationship, that occur from initiation of study medication until 4 weeks after last administration of study IMP must be reported to the CRF/eCRF database as instructed.

Any SAEs and deaths that occur after the post treatment follow-up visit but within 30 days of the last dose of study IMP, regardless of causality, should also be reported.

All AEs should be followed up until resolution if possible. If by the last day on study (including the off-study medication follow-up period) the AE has not resolved, then the AE will be followed up until the investigator and/or Gilead Sciences determine that the subject's condition is stable. However, Gilead Sciences may request that certain AEs be followed until resolution.

Investigators are not obligated to actively seek SAEs after the 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 DSPH.

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

- At the time of study start, SAEs will be reported using a paper serious adverse event reporting form. During the study conduct, sites may transition to an electronic SAE (eSAE) system. Gilead will notify sites in writing and provide training and account information prior to implementing an eSAE system.

Serious Adverse Event Paper Reporting Process

- All SAEs will be recorded on the serious adverse event report form and submitted by faxing the report form within 24 hours of the investigator’s knowledge of the event to the attention of PPD PVG.

PPD PVG – North America	Phone: +1 888 483 7729 Fax: +1 888 529 3580
PPD PVG – Europe, Asia Pacific, and Africa	Phone: +44 1223 374240 Fax: +44 1223 374102
PPD PVG – Latin America	Phone: +55 11 4504 4801 Fax: +01 800 248 0608
GSI Drug Safety and Public Health (DSPH):	Fax: +1 (650) 522-5477 E-mail:safety_fc@gilead.com
Gilead Sciences Medical Monitor:	Name Erin Quirk, M.D. Telephone: PPD Mobile Phone: PPD Fax: PPD E-mail: PPD

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 DSPH 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 as described above.
- 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 CRF/eCRF database within the timelines outlined in the CRF/eCRF completion guideline.
- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead DSPH 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 as described above.

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

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

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

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

- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's CRF/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. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

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

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

- Severity should be recorded and graded according to the GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities. 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. 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 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.

- When restarting investigational medicinal product following resolution of the adverse event, the investigational medicinal product should be restarted at full dose upon discussion with the Medical Monitor.

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

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

7.5.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

Continue investigational medicinal product at the discretion of the Investigator.

7.5.2. Grade 3 Laboratory Abnormality or Clinical Event

- For Grade 3 clinically significant laboratory abnormality or clinical event, investigational medicinal product may be continued if the event is considered to be unrelated to investigational medicinal product.

- For a Grade 3 clinical event, or clinically significant laboratory abnormality confirmed by repeat testing, that is considered to be related to investigational medicinal product, investigational medicinal product should be withheld until the toxicity returns to ≤ Grade 2.

- If a laboratory abnormality recurs to ≥ Grade 3 following rechallenge with investigational medicinal product and is considered related to investigational medicinal product, then investigational medicinal product should be permanently discontinued and the subject managed according to local practice. Recurrence of laboratory abnormalities considered unrelated to investigational medicinal product may not require permanent discontinuation.

7.5.3. Grade 4 Laboratory Abnormality or Clinical Event

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

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

7.6. Toxicity Management

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

- Grade 3 and Grade 4 clinically significant laboratory abnormalities should be confirmed by repeat testing within three calendar days of receipt of results and before study drug 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 Gilead Sciences Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 5).

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

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

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

7.7. Special Situations Reports

7.7.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, lack of effect reports and pregnancy reports regardless of an associated AE. Also includes reports of adverse reactions in infants following exposure from breastfeeding, and reports of adverse reactions associated with product complaints and reports arising from occupational exposure. A pregnancy report is used to report any pregnancy following maternal or paternal exposure to the medicinal product.

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 or 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.

7.7.2. Instructions for Reporting Special Situations

7.7.2.1. Instructions for Reporting Pregnancies

The investigator should report all pregnancies that are identified after the subject first consents to participate in the study (ie, signs the informed consent) and throughout the study, including the post study drug follow-up period, to the PPD PVG using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

Refer to Section 7.3 and the CRF/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 7.1.2. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to PPD PVG.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to PPD PVG 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 DSPH. Gilead DSPH contact information is as follows: Email: Safety_FC@gilead.com and Fax: +1 (650) 522-5477.

Refer to Section 7.8 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Recommendations.

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 PPD PVG within 24 hours of the investigator becoming aware of the situation.

These reports must consist of situations that involve study IMP, but do not apply to concomitant medications. Except for situations that result in AEs, special situations involving concomitant medications will not be reported. Any inappropriate use of medications prohibited by this protocol should not be reported as “misuse,” but may be more appropriately documented as a protocol deviation.

Refer to Section 7.4 and the CRF/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 CRF/eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

7.8. Risks for Females of Childbearing Potential or During Pregnancy

The risks of treatment with the study drug during pregnancy have not been evaluated. If females are using hormonal agents for contraception, the safety and/or efficacy may be

affected by possible drug-drug interactions. The plasma concentration of the hormonal contraceptive ethinyl estradiol may be decreased when used concomitantly with EVG in combination with ritonavir-boosted protease inhibitors. It is recommended that a non-hormonal method (or methods) be used concurrently with hormonal contraceptives. If females utilize hormonal agents as one of their contraceptive methods, it is required that the same hormonal method be used for at least 3 months before study dosing. Please refer to the latest version of the Investigator's Brochure for additional information.

7.8.1. Definition of Childbearing Potential and Post-Menopausal

A female subject of childbearing potential is a nonmenopausal female who has not had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure. This definition includes a young woman who has not yet started menstruating (premenarchal, Tanner Stage 3 and below). Pre-pubertal females (Tanner Stages 1 and 2) are not considered to be of childbearing potential unless onset of menarche has occurred.

Menopause can be assumed to have occurred in a woman when there is:

- Appropriate medical documentation of prior complete bilateral oophorectomy (i.e., surgical removal of the ovaries, resulting in "surgical menopause" and occurring at the age at which the procedure was performed)

7.8.2. Contraception Requirements for Males and Females of Childbearing Potential

Male subjects and female subjects of childbearing potential must agree to utilize protocol-recommended methods of contraception from the Screening Visit throughout the study period and for 30 days after administration of the last dose of study drug. Female study subjects who are not heterosexually active must have periodic confirmation of continued abstinence from heterosexual intercourse and regular pregnancy testing while taking EVG. The investigator should counsel subjects on the protocol-recommended method(s) for avoiding pregnancy in case subject chooses to engage in heterosexual intercourse. These methods are recommended due to the low failure rate (ie, less than 1% per year). See Table 7-1 for the protocol-recommended methods.

Females of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline/Day 1 prior to receiving the first dose of study drug. Lactating females must discontinue nursing before investigational medicinal product administration.

Table 7-1. Protocol-Recommended Contraceptive Methods

Methods to Use by Themselves	Combination Methods	
	Hormone Methods (choose one and use with a barrier method)	**Barrier Methods (use both OR choose one and use with a hormone method)**
Intra-uterine devices (IUDs) • Copper T 380A IUD • LNg 20 IUD	**Estrogen and Progesterone** • Oral contraceptives • Transdermal patch • Vaginal ring **Progesterone** • Injection • Implant	• Diaphragm OR • Cervical cap • Male condom (without spermicide)
	Partner's vasectomy must be used along with a hormone or barrier method.	

Acceptable barrier methods include: diaphragm, cervical cap, and the male condom. Female subjects who utilize hormonal contraceptives as one of their birth control methods must have used the same method for at least 3 months before study dosing. If females are using hormonal agents for contraception, the efficacy may be affected by possible drug-drug interaction. The plasma concentration of the hormonal contraceptive ethinyl estradiol may be decreased when used concomitantly with EVG in combination with ritonavir-boosted protease inhibitors. It is recommended that non-hormonal methods be used concurrently. Other contraceptive methods may be acceptable after discussion with the Medical Monitor.

Male subjects who are sexually active must be willing to use effective barrier contraception (e.g., non-lambskin condoms) during heterosexual intercourse from screening through completion of the study and continuing for at least 30 days after the last dose of study drug. In addition, male subjects must refrain from sperm donation from Day 0 through completion of the study and continuing for at least 30 days after administration of the last dose of study drug.

All subjects of child bearing potential must undergo appropriate contraceptive counselling. The Investigator should counsel subjects on the most effective method(s) for avoiding pregnancy during the study.

Use of condoms (except for lambskin condoms) should be encouraged for all participants with the potential to be sexually active because they have been proven to decrease the risk of transmission of HIV and other sexually transmitted diseases.

7.8.3. Procedures to be Followed in the Event of Pregnancy

Subjects should be instructed to notify the Investigator if they become pregnant at any time during the study, or if they become pregnant within 30 days of last study drug dose. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the Investigator and discontinue study drug immediately. The Investigator should report all pregnancies to PPD PVG using the Pregnancy Report form within 24 hours of becoming aware of the pregnancy. The Investigator should counsel the subject regarding the possible effects of prior study drug exposure on the fetus and the need to inform the study site of the outcome of the pregnancy.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary analysis objectives of this study are:

- To evaluate the steady-state PK and confirm the dose of EVG/r in HIV-1 infected, antiretroviral treatment-experienced subjects 4 weeks to <18 years of age
- To evaluate the safety and tolerability of EVG/r in HIV-1 infected, antiretroviral treatment-experienced subjects 4 weeks to <18 years of age

The secondary analysis objective of this study is:

- To evaluate the antiviral activity of EVG/r in HIV-1 infected, antiretroviral treatment-experienced subjects 4 weeks to <18 years of age who are failing their current HAART regimen

8.1.2. Primary Endpoint

The primary endpoints are PK parameters AUC_{tau} and C_{max} of EVG and the incidence of treatment-emergent AEs and treatment-emergent laboratory abnormalities.

8.1.3. Secondary Endpoint

The secondary endpoints include:

- PK parameters C_{tau}, CL/F, and Vz/F of EVG
- The percentage of subjects with plasma HIV-1 RNA < 50 and < 400 copies/mL at Weeks 24 and 48 as defined by the FDA snapshot analysis, respectively
- The change from baseline in plasma $\log_{10}$ HIV-1 RNA (copies/mL) and in CD4+ cell count (cells/µL), and CD4 percentage at Weeks 24 and 48
- Tanner Stages at Weeks 24 and 48, and age of first menses.
- Palatability of oral suspension formulation of EVG in appropriate age group
- Adherence to EVG

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Efficacy

Efficacy analysis will be conducted to use the full analysis set (FAS), which will include all subjects who were enrolled and received at least one dose of study drug.

8.2.1.2. Safety

Safety analysis will be conducted to use the safety analysis set, which will include all subjects who were enrolled and received at least one dose of study drug.

All the data collected up to 30 days after subjects permanently discontinue their study regimen will be included in the safety summaries.

8.2.1.3. Pharmacokinetics (PK)

Intensive PK Analysis Set

The intensive PK analysis set for Part A will include all Part A subjects who were enrolled and received at least one dose of study drug and for whom steady-state pharmacokinetic profiles of EVG at Intensive PK visit are evaluable. The intensive PK analysis set will be used for detailed PK analysis of EVG.

PK Analysis Set

The PK analysis set will include all subjects with HIV-1 RNA > 1,000 copies/mL at screening and were enrolled and received at least one dose of study drug and for whom at least one observed concentration data of EVG is available. The PK analysis set will be used for analysis of general PK and trough blood concentrations.

8.2.2. Subject Groups

Intensive PK Group: includes all Part A subjects.

Long-Term Safety Group: includes all Part A subjects with HIV-1 RNA >1,000 copies/mL at screening and all Part B subjects.

PK and safety analysis will be conducted by age group and overall for the intensive PK group and the long-term safety group. Efficacy analysis will be conducted by age group and overall for subjects with HIV-1 RNA < 50 copies/mL at screening and for subjects with HIV-1 RNA > 1,000 copies/mL at screening.

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.

The PK concentration values below the limit of quantitation (BLQ) will be treated as zero for the determination of summary and order statistics. Individual values that are BLQ will be presented as "BLQ" in the concentration data listing and will be excluded in any calculation of geometric means or ratios.

Subjects aged 6 months to < 2 years old (Cohort 4a) and subjects aged 4 weeks to < 6 months old (Cohort 4b) in Part A will be combined into one age group (Cohort 4) in Part A for the safety analysis, and will be summarized separately and combined for PK evaluation.

8.4. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized using standard descriptive methods by age group and overall for the intensive PK group and the long-term safety group.

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

Baseline data will include a summary of body weight, height, body mass index, HIV-1 infection, CD4 counts, and eGFR.

8.5. Efficacy Analysis

The percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 24 (Windows: Study Days 141-196) as defined by the FDA snapshot analysis algorithm will be summarized using descriptive statistics.

Virologic outcome at Week 24 will be defined into the following 3 categories:

- Virologic Success: this includes subjects who have the last available on study drug HIV-1 RNA < 50 copies/mL in the Week 24 window;
- Virologic Failure: this includes (1) subjects who have the last available on study drug HIV-1 RNA ≥ 50 copies/mL in the Week 24 window, (2) subjects who discontinue prior to or in the Week 24 window due to lack of efficacy, or (3) subjects who discontinue prior to or in the Week 24 window due to reasons other than AE, death, and lack of efficacy and have the last available on study drug HIV-1 RNA ≥ 50 copies/mL;
- No Virologic Data in the Week 24 window due to:
  - Discontinuation of study drug prior to or in the Week 24 window due to AE or death; or

— Discontinuation of study drug prior to or in the Week 24 window due to reasons other than AE, death, or lack of efficacy and the last available on study drug HIV-1 RNA < 50 copies/mL; or

— Missing data in the Week 24 window but on study drug

Virologic outcomes will be summarized using frequency counts and percentages based on the FAS analysis set by age group and overall for subjects with HIV-1 RNA >1,000 copies/mL at screening. The 95% confidence intervals for the percentage estimate will be constructed using the Exact method.

The percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 (Windows: Study Days 309-378) and the percentage of subjects with HIV-1 RNA < 400 copies/mL at Weeks 24 and 48 will be summarized in the same manner as described above.

The relationship between EVG exposures (AUC_{tau}, C_{max}, and C_{tau}) and virologic failures as defined by the snapshot algorithm will be explored among subjects who have non-missing AUC_{tau}, C_{max}, or C_{tau} for EVG and virologic failure data.

The changes from baseline in plasma $\log_{10}$ HIV-1 RNA, CD4+ cell count, and CD4 percentage will be summarized using descriptive statistics by age group and overall for subjects with HIV-1 RNA < 50 copies/mL at screening and for subjects with HIV-1 RNA >1,000 copies/mL at screening. In addition, the change from baseline in CD4 percentage will be summarized by visit for subjects < 5 years of age for subjects with HIV-1 RNA < 50 copies/mL at screening and for subjects with HIV-1 RNA > 1,000 copies/mL at screening.

8.6. Safety Analysis

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

8.6.1. Extent of Exposure

Duration of exposure to study drug will be expressed as the number of weeks between the first and last dose of the study regimen, inclusive, regardless of temporary interruptions in study regimen administration by age group and overall for subjects with HIV-1 RNA < 50 copies/mL at screening and for subjects with HIV-1 RNA > 1,000 copies/mL at screening.

Dosing information for individual subjects will be listed.

Palatability of oral suspension formulation of EVG will be summarized using descriptive statistics by appropriate age group and overall.

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.

Adverse events meeting one of the following criteria are defined as treatment-emergent AEs.

1. Events with onset dates on or after the start of treatment and up to 30 days after the permanent discontinuation of the study medication from each specified study phase, and

2. The continuing adverse events diagnosed prior to the start of treatment and worsening in severity grade, or non-serious adverse events at baseline become serious, or adverse events resulting in treatment discontinuation after the start of treatment.

Summaries (number and percentage of subjects) of treatment-emergent adverse events (by SOC and PT) will be provided by age group and overall for the intensive PK group and the long-term safety group. Additional summaries will include summaries for adverse events by grade, Investigator's assessment of relationship to study drug, and effect on study drug dosing.

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 by age group and overall for the intensive PK group and the long-term safety group .

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

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 investigational medicinal product plus 30 days, will be summarized by age group and overall for the intensive PK group and the long-term safety group. If baseline data are missing, then any graded abnormality (i.e., at least a Grade 1) will be considered treatment emergent. The maximum toxicity grade will be summarized by laboratory parameter.

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

8.6.4. Other Safety Evaluations

8.6.4.1. Tanner Stage Assessment

Tanner Stages at Weeks 24 and 48 will be summarized by baseline Tanner Stage using frequency and percentage. Age of first menses will be summarized descriptively.

8.7. Pharmacokinetic Analysis

For the intensive PK analysis set, the concentration data of EVG over sampling time will be listed and summarized. Pharmacokinetic parameters (e.g., AUC_{tau}, AUC_{last}, C_{max}, T_{max}, C_{last}, T_{last}, C_{tau}, λz, CL/F, Vz/F and T½) will be listed and summarized for EVG using descriptive statistics (e.g., sample size, arithmetic mean, geometric mean, coefficient of variation %, standard deviation, median, Q1, Q3, minimum, and maximum) by age group and overall. Plasma concentrations over time will be plotted in semilogarithmic and linear formats as mean ± standard deviation, and median (Q1, Q3).

To evaluate the exposures of EVG achieved in pediatric subjects are similar to the exposures observed in historical control subjects, an analysis of variance (ANOVA) will be carried out for log-transformed AUC_{tau} and C_{max} of EVG as the primary endpoints while C_{tau} of EVG will be explored for the intensive PK analysis set. EVG exposure data from the current study will be compared to the integrated historical control data using pharmacokinetic equivalence testing with an equivalency boundary of 70% - 143% for the 90% confidence interval. In addition, the 95% confidence interval of the geometric mean estimate of CL/F and Vz/F of EVG will be provided for the intensive PK analysis set.

8.8. Sample Size and Power

A total of 12 pediatric subjects in each cohort compared to 334 HIV-infected historical control subjects included in the EVG population modeling will provide at least 90% power to conclude exposure equivalence of EVG AUC_{tau} and C_{max} in pediatric subjects vs. in historical control subjects, assuming the expected geometric mean ratio is 1, equivalency boundary is 70% to 143%, two one-sided tests are each performed at an alpha level of 0.05, and the standard deviation is 0.36 ng•hr/mL for AUC_{tau} and 0.28 ng/mL for C_{max} (natural log scale, estimated from EVG population PK modeling).

A total of 12 subjects in each cohort will also provide at least 80% power to target a 95% confidence interval within 60% and 140% of the geometric mean estimate of clearance and volume of distribution of EVG, respectively, assuming a coefficient of variation (CV) of 42.3% for clearance and 22.9% for volume of distribution (estimated from EVG population PK modeling).

A total of 50 subjects from Parts A and B combined will provide for reasonable assessment of safety through Week 48 over the age range 4 weeks to < 18 years. For the main efficacy endpoint, assuming a virologic success rate of 60% (based on Study GS-US-183-0145 in adults) in this population of antiretroviral treatment-experienced subjects receiving a new class drug, i.e., EVG, a sample size of 50 subjects will result in a 95% confidence interval (CI) for the response rate from 46% to 74% (i.e., an error margin of 14%).

Sample size and power calculations were made using the software package nQuery Advisor (Version 6.0).

8.9. Data Monitoring Committee

An external multidisciplinary data monitoring committee (DMC) will review the progress of the study and perform interim reviews of safety and PK data and provide recommendation to Gilead about whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications.

The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct and meeting schedule.

While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of 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, "Protection of Human Subjects", and 21 CFR, part 56, "Institutional Review Boards".

The investigator and all applicable subinvestigators will comply with 21 CFR, Part 54, "Financial Disclosure by Clinical Investigators", 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 or IEC local requirements.

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 or IEC, or laboratory. Laboratory specimens must be labeled in such as way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions detailed in the study laboratory manual. 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, CRF/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 (if applicable), IRB or 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 will be completed by an authorized study staff member whose training for this function is documented according to study procedures. eCRF should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), 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. The eCRF capture the data required per the protocol schedule of events and procedures. 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). 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 or 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 or IEC in accordance with local requirements and receive documented IRB or 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. 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 CRF/eCRF.

The monitor is responsible for routine review of the CRF/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 CRF/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.

9.3.2. 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.

9.3.3. 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.

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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 2/3 Multicenter, Open-Label, Multicohort, Two-Part Study Evaluating the Pharmacokinetics (PK), Safety, and Antiviral Activity of Elvitegravir (EVG) Administered with a Background Regimen (BR) Containing a Ritonavir-Boosted Protease Inhibitor (PI/r) in HIV-1 Infected, Antiretroviral Treatment-Experienced Pediatric Subjects

GS-US-183-0160 Protocol

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

ERIN QUIRK

Erin Quirk, MD
Medical Monitor

PPD

Signature

26-Apr-2013

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 – Cohorts 1, 2, and 3

**COHORT 1 (12 to < 18 years old);
COHORT 2 (6 to < 12 years old);
COHORT 3 (2 to < 6 years old)**

Study Procedures	Screening[a]	Baseline (Day 1)[b]	Week 1 (Day 7)[c]	Day 10[b,d]	Week 3[c]	Week 4[e]	End of Week[f]							Post Week 48	30-Day Follow-up[g]	ESDD[h]
							8	12	16	24	32	40	48	Every 12 weeks		
Assent/Informed Consent	X															
Medical History[i]	X															
Adverse Events[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[k]	X	X		X		X	X	X	X	X	X	X	X	X	X	X
Complete[l]/Symptom-Directed Physical Exam	**X**	**X**		X		X	X	X	X	**X**	X	X	**X**	X	X	**X**
Height/Length	X	X						X		X			X	X		X
Body Weight	X	X		X		X	X	X	X	X	X	X	X	X	X	X
Tanner Stage Evaluations[m]		X								X			X	X		
12-lead ECG (supine)	X															X

**COHORT 1 (12 to < 18 years old);
COHORT 2 (6 to < 12 years old);
COHORT 3 (2 to < 6 years old)**

Study Procedures	Screening[a]	Baseline (Day 1)[b]	Week 1 (Day 7)[c]	Day 10[b,d]	Week 3[c]	Week 4[e]	End of Week[f]							Post Week 48	30-Day Follow-up[g]	ESDD[h]
							8	12	16	24	32	40	48	Every 12 weeks		
HIV-1 Genotype[n]	X															
Hematology Profile[o]	X	X		X[b]		X	X	X	X	X	X	X	X	X	X	X
Chemistry Profile[p]	X	X		X[b]		X	X	X	X	X	X	X	X	X	X	X
CD4+ Cell Count and Percentage	X	X				X	X	X	X	X	X	X	X	X	X	X
Metabolic Assessments[q]		X								X			X	X		
Plasma HIV-1 RNA	X	X		X[b]		X	X	X	X	X	X	X	X	X	X	X
Plasma Storage Sample[r]		X						X		X			X	X		X
HBV and HCV Serologies[i]	X															
Estimated Glomerular Filtration Rate[s]	X	X		X[b]		X	X	X	X	X	X	X	X	X		X
Urinalysis	X	X		X[b]		X		X		X			X	X	X	X

**COHORT 1 (12 to < 18 years old);
COHORT 2 (6 to < 12 years old);
COHORT 3 (2 to < 6 years old)**

Study Procedures	Screening[a]	Baseline (Day 1)[b]	Week 1 (Day 7)[c]	Day 10[b,d]	Week 3[c]	Week 4[e]	End of Week[f]							Post Week 48	30-Day Follow-up[g]	ESDD[h]
							8	12	16	24	32	40	48	Every 12 weeks		
Urine Storage Sample[t]		X		X[b]		X		X		X			X	X	X	X
Serum Pregnancy Test[u]	X															
Urine Pregnancy Test[u]		X		X		X	X	X	X	X	X	X	X	X	X	X
Palatability Assessments[v]		X		X						X			X			
Dispense Diary Cards[b]		X														
Review Diary Cards[b]			X	X												
Single PK Sampling[w]						X	X	X			X			X		
Trough PK Sample[x]									X			X				
Intensive PK Sampling[y]				X												
Study Drug Dispensation		X				X	X	X	X	X	X	X	X	X		

**COHORT 1 (12 to < 18 years old);
COHORT 2 (6 to < 12 years old);
COHORT 3 (2 to < 6 years old)**

Study Procedures	Screening[a]	Baseline (Day 1)[b]	Week 1 (Day 7)[c]	Day 10[b,d]	Week 3[c]	Week 4[e]	End of Week[f]							Post Week 48	30-Day Follow-up[g]	ESDD[h]
							8	12	16	24	32	40	48	Every 12 weeks		
In-clinic Dosing[z]		X		X					X			X				
Drug Accountability				X		X	X	X	X	X	X	X	X	X		X

a Evaluations to be completed within 35 days prior to baseline (or 42 days for subjects who require repeat testing of the HIV-1 genotype or if the screening visit is divided into multiple visits).

b Part A only.

c Week 1 (Day 7) and Week 3 are telephone visits only, to be completed ± 2 days from the protocol specified date.

d If subject weighs <18 kg at the Baseline/Day 1 visit, the Day 10 intensive PK will be divided into separate visits. Safety and HIV-1 RNA assessments will be completed up to 3 days prior to Day 10 (eg, Day 7). Intensive PK sampling will be completed on Day 10. If the subject has already dosed prior to the Day 10 clinic visit or is not in a fasted state, the Day 10 assessments must not be completed. The subject should be instructed to return within + 4 days (Days 11, 12, 13, or 14) for the PK visit. If dosing non-compliance not related to an AE is identified on or prior to the Day 10 visit, the Day 10 intensive PK assessments must not be completed. The subject should be counseled regarding proper dosing and asked to return for the intensive PK visit no sooner than 3 days following compliant dosing and no later than Day 14 (i.e., return on Day 13 or Day 14). If dosing non-compliance due to an AE is identified on or prior to the Day 10 visit, the Day 10 intensive PK assessments must not be completed. Consultation with the Gilead Medical Monitor is required regarding the potential of rescheduling the Day 10 intensive PK visit.

e Week 4 visit is to be completed 31 to 33 days from the Baseline visit.

f Study visits to be completed ± 2 days for Week 8 and ± 4 days for Week 12 through Week 48 of the protocol specified date from the Baseline visit.

g 30-Day Follow-up visit to be completed as follows: 30 days after the last dose taken following the Day 10 PK evaluation for subjects with suppressed viremia (HIV-1 RNA <50 copies/mL at screening); 30 days after the ESDD visit for subjects who permanently discontinue study drug prior to Day 10; 30 days after the ESDD visit for subjects who permanently discontinue study drug during the 48 weeks of dosing and do not wish to continue in the study; 30 days after the Week 48 visit for subjects who complete 48 weeks on study drug and do not wish to enroll in the extension study.

h ESDD visit should occur within 72 hours of last dose of study drug.

i **For Cohort 3 only**, maternal medical history for Hepatitis B and C will be obtained in lieu of laboratory testing.

j Any adverse event or test showing abnormal results that is believed to be possibly/probably related to study drug treatment will be re-evaluated weekly (or as often as deemed prudent by the investigator) until the abnormality is resolved, returns to baseline, or is otherwise explained.

k Vital signs include blood pressure, temperature, heart rate, and respiration rate.

l Perform complete physical examinations at Screening, Baseline, Weeks 24, 48 and ESDD visits.

m Tanner Stage assessments (Appendix 6) will be performed for subjects ≥ 6 years of age at the time of the visit, until the subject has been documented as Tanner Stage 5. Tanner Stage assessments will be performed every 48 weeks in the extension phase of the study or until subjects reach Tanner Stage 5, after which point Tanner assessments will no longer be performed.

n Genotypic analysis for reverse transcriptase, protease, and integrase resistance will be done at screening for subjects with HIV-1 RNA >1,000 copies/mL. The investigator must have received the results from the screening genotype before proceeding with the Baseline visit. Historical genotypes should be obtained for subjects with HIV-1 RNA <50 copies/mL at screening.

o CBC with differential and platelet count.

p Chemistry profile: Albumin, alkaline phosphatase, AST, ALT, direct bilirubin, total bilirubin, bicarbonate, BUN, calcium, chloride, CPK, creatinine, magnesium, phosphorus, potassium, total protein, sodium, uric acid, amylase and lipase

q Fasting glucose and lipid panel (total cholesterol, HDL, direct LDL, and triglycerides) metabolic assessments will be performed for subjects failing a current antiretroviral regimen (HIV-1 RNA >1,000 copies/mL) at screening and weighing ≥13 kg at the time of the visit, for the following visits: Baseline, Weeks 24, 48, ESDD, and every 48 weeks in the extension phase of the study. 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. **For Cohorts 2 and 3 only**, direct LDL will be calculated if subjects weigh <15.8 kg at the time of the visit.

r Plasma storage samples banked for possible future protocol-related testing (virology, PK analysis). **For Cohort 3 only**, plasma storage samples are collected at Weeks 12, 24, 48, ESDD, and every 12 weeks in the extension phase of the study.

s eGFR using Schwartz Formula (mL/min/1.73m^2) = k × L/Scr [(k is a proportionality constant, refer to Section 4.2 for details); L is height in centimeters (cm); and Scr is serum creatinine (mg/dL)]

t Urine storage samples banked for possible future protocol-related testing (Urine chemistry including urine phosphorus and urine creatinine)

u Females of childbearing potential only.

v Palatability of EVG suspension formulation will be assessed at Baseline/Day 1, Day 10 (**Part A only**), Week 24, and Week 48, as applicable.

w Single PK sampling at Week 12 is **only for Cohorts 1 and 2.**

x A trough (20 to 24 hours postdose) plasma PK sample will be collected. Subjects must come into the clinic without taking their dose of EVG and the PI/r and other BR components.

y Intensive PK sampling will be performed on Day 10 and **only applicable for subjects in Part A**. Subjects must come into the clinic without taking their dose of EVG and the PI/r and other BR components. For Cohorts 2 and 3, samples will be collected at 0 (predose, ≤ 30 minutes), 1.5, 2.5, 3.5, 5, 8, 10, and 12 hours postdose. Please refer to the PK manual for details.

z All subjects will be given their dose of EVG + PI/r and other BR components with food in the clinic at Baseline, Day 10, Weeks 16 and 40.

Appendix 3. Study Procedures Table – Cohort 4

COHORT 4 (4 weeks to < 2 years old)																
							End of Week[ff]							Post Week 48		
Study Procedures	**Screening[a]**	**Baseline (Day 1)**	**Week 1 (Day 7)[b]**	**Day 10[cc,dd]**	**Week 3[bb]**	**Week 4[ee]**	**8**	**12**	**16**	**24**	**32**	**40**	**48**	**Every 12 weeks**	**30-Day Follow-up[gg]**	**ESDD[h]**
Visit to be divided if subject weighs <9.4 kg at visit?[ii]	Y^{jj}	Y^{kk}	N	Y^{ll}	N	Y^{jj}	Y^{jj}	Y^{jj}	N	Y^{jj}	Y^{jj}	Y^{jj}	Y^{jj}	Y^{jj}	Y^{jj}	Y^{jj}
Assent/Informed Consent	X^{1}															
Medical History[mm]	X^{1}															
Adverse Events[nn,oo]	$X^{1,2}$	$X^{0,1}$	X	$X^{0,1,2}$	X	$X^{1,2}$	$X^{1,2}$	$X^{1,2}$	X	$X^{1,2}$	$X^{1,2}$	$X^{1,2}$	$X^{1,2}$	$X^{1,2}$	$X^{1,2}$	$X^{1,2}$
Concomitant Medications[oo]	$X^{1,2}$	$X^{0,1}$	X	$X^{0,1,2}$	X	$X^{1,2}$	$X^{1,2}$	$X^{1,2}$	X	$X^{1,2}$	$X^{1,2}$	$X^{1,2}$	$X^{1,2}$	$X^{1,2}$	$X^{1,2}$	$X^{1,2}$
Vital Signs[pp]	X^{1}	X^{0}		X^{0}		X^{1}	X^{1}	X^{1}	X	X^{1}	X^{1}	X^{1}	X^{1}	X^{1}	X^{1}	X^{1}
Complete[qq]/Symptom-Directed Physical Exam	X^{1}	$\mathbf{X^{0}}$		X^{0}		X^{1}	X^{1}	X^{1}	X	X^{1}	X^{1}	X^{1}	X^{1}	X^{1}	X^{1}	$\mathbf{X^{1}}$
Height/Length[rr]	X^{1}	X^{0}				X^{1}	X^{1}	X^{1}	X	X^{1}	X^{1}	X^{1}	X^{1}	X^{1}		X^{1}
Body Weight	X^{1}	X^{0}		X^{0}		X^{1}	X^{1}	X^{1}	X	X^{1}	X^{1}	X^{1}	X^{1}	X^{1}	X^{1}	X^{1}

COHORT 4 (4 weeks to < 2 years old)																
							End of Week[ff]							Post Week 48		
Study Procedures	**Screening[a]**	**Baseline (Day 1)**	**Week 1 (Day 7)[b]**	**Day 10[cc,dd]**	**Week 3[bb]**	**Week 4[ee]**	**8**	**12**	**16**	**24**	**32**	**40**	**48**	**Every 12 weeks**	**30-Day Follow-up[gg]**	**ESDD[h]**
Visit to be divided if subject weighs <9.4 kg at visit?[ii]	Y^{ij}	Y^{kk}	N	Y^{ll}	N	Y^{ij}	Y^{ij}	Y^{ij}	N	Y^{ij}	Y^{ij}	Y^{ij}	Y^{ij}	Y^{ij}	Y^{ij}	Y^{ij}
Tanner Stage Evaluations[ss]														X		
12-lead ECG (supine)	X^1															X^1
HIV-1 Genotype[tt]	X^2															
Hematology Profile[uu]	X^1	X^0		X^0		X^1	X^1	X^1	X	X^1	X^1	X^1	X^1	X^1	X^1	X^1
Chemistry Profile[vv]	X^1	X^0		X^0		X^1	X^1	X^1	X	X^1	X^1	X^1	X^1	X^1	X^1	X^1
CD4+ Cell Count and Percentage	X^1	X^0				X^1	X^1	X^1	x	X^1	X^1	X^1	X^1	X^1	X^1	X^1
Metabolic Assessments[ww]		X^0								X^1			X^1	X^1		
Plasma HIV-1 RNA	X^2	X^1		X^2		X^2	X^2	X^2	X_2	X^2	X^2	X^2	X^2	X^2	X^2	X^2
Plasma Storage Sample[xx]														X		

COHORT 4 (4 weeks to < 2 years old)																
							End of Week[ff]							Post Week 48		
Study Procedures	**Screening[a]**	**Baseline (Day 1)**	**Week 1 (Day 7)[b]**	**Day 10[cc,dd]**	**Week 3[bb]**	**Week 4[ee]**	**8**	**12**	**16**	**24**	**32**	**40**	**48**	**Every 12 weeks**	**30-Day Follow-up[gg]**	**ESDD[h]**
Visit to be divided if subject weighs <9.4 kg at visit?[ii]	Y[ij]	Y[kk]	N	Y[ll]	N	Y[ij]	Y[ij]	Y[ij]	N	Y[ij]	Y[ij]	Y[ij]	Y[ij]	Y[ij]	Y[ij]	Y[ij]
Estimated Glomerular Filtration Rate[yy]	X^1	X^0		X^0		X^1	X^1	X^1	X	X^1	X^1	X^1	X^1	X^1		X^1
Urinalysis	X^1	X^0		X^0		X^1		X^1		X^1			X^1	X^1	X^1	X^1
Urine Storage Sample[zz]		X^0		X^0		X^1		X^1		X^1			X^1	X^1	X^1	X^1
Urine Pregnancy Test[aaa]														X		
Palatability Assessments[bbb]		X		X						X			X			
Dispense Diary Cards[cc]		X^1														
Review Diary Cards[cc]			X	X^1												
Single PK Sampling						X^2	X^2	X^2			X^2			X^2		
Trough PK Sample[ccc]									X			X^2				

COHORT 4 (4 weeks to < 2 years old)																
							End of Week[ff]							Post Week 48		
Study Procedures	**Screening[a]**	**Baseline (Day 1)**	**Week 1 (Day 7)[b]**	**Day 10[cc,dd]**	**Week 3[bb]**	**Week 4[ee]**	**8**	**12**	**16**	**24**	**32**	**40**	**48**	**Every 12 weeks**	**30-Day Follow-up[gg]**	**ESDD[h]**
Visit to be divided if subject weighs <9.4 kg at visit?[ii]	Y[jj]	Y[kk]	N	Y[ll]	N	Y[jj]	Y[jj]	Y[jj]	N	Y[jj]	Y[jj]	Y[jj]	Y[jj]	Y[jj]	Y[jj]	Y[jj]
Intensive PK Sampling[ddd]				X[1]												
Study Drug Dispensation		X[1]				X[1]	X[1]	X[1]	X	X[1]	X[1]	X[1]	X[1]	X[1]		
In-clinic Dosing[eee]		X[1]		X[1]					X			X[1]				
Drug Accountability				X[1]		X[1]	X[1]	X[1]	X	X[1]	X[1]	X[1]	X[1]	X[1]		X[1]

aa Evaluations to be completed within 35 days prior to baseline (or 42 days for subjects who require repeat testing of the HIV-1 genotype or if the screening visit is divided into multiple visits).

bb Week 1 (Day 7) and Week 3 are telephone visits only, to be completed ± 2 days from the protocol specified date.

cc Part A only.

dd In Cohort 4, fasting is not required for the Day 10 intensive PK evaluation. If dosing non-compliance not related to an AE is identified on or prior to the Day 10 visit, the Day 10 intensive PK assessments must not be completed. The subject should be counseled regarding proper dosing and asked to return for the intensive PK visit no sooner than 3 days following compliant dosing and no later than Day 14 (i.e., return on Day 13 or Day 14). If dosing non-compliance due to an AE is identified on or prior to the Day 10 visit, the Day 10 intensive PK assessments must not be completed. Consultation with the Gilead Medical Monitor is required regarding the potential of rescheduling the Day 10 intensive PK visit.

ee Week 4 visit is to be completed 31-33 days from the Baseline visit.

ff Study visits are to be completed ± 2 days for Week 8 and ± 4 days for Week 12 through Week 48 of the protocol specified date from the Baseline visit.

gg 30-Day Follow-up visit to be completed as follows: 30 days after the last dose taken following the Day 10 PK evaluation for subjects with suppressed viremia (HIV-1 RNA <50 copies/mL at screening); 30 days after the ESDD visit for subjects who permanently discontinue study drug prior to Day 10; 30 days after the ESDD visit for subjects who permanently discontinue study drug during the 48 weeks of dosing and do not wish to continue in the study; 30 days after the Week 48 visit for subjects who complete 48 weeks on study drug and do not wish to enroll in the extension study.

hh ESDD visit should occur within 72 hours of last dose of study drug.

ii For subjects weighing < 9.4 kg at each visit, the study visit will be divided into separate visits. The first visit should occur according to the protocol specified visit date, with a visit window of ± 2 days up to Week 8 and ± 4 days through Week 48. The second visit should occur up to 7 days from the first visit. **Please refer to footnotes KK and LL for exceptions to the Baseline/Day 1 and Day 10 visits, respectively.**

jj X^1 = assessments to be performed at the first visit; X^2 = assessments to be performed at the second visit, to be completed up to 7 days from the first visit

kk The Baseline/Day 1 visit will be divided into a Pre-Baseline visit and a Baseline/Day 1 visit if subjects weigh <9.4 kg at the Screening visit. X^0 = assessments to be performed at the Pre-Baseline visit, to be completed 3-5 days prior to the Baseline visit; X^1 = assessments to be performed at the Baseline visit.

ll The Day 10 intensive PK visit will be divided into 3 visits (Day 7 [instead of a telephone visit], Day 10, and Day 14) if subjects weigh <9.4 kg at the Baseline/Day 1 visit. X^0 = assessments to be performed at the Day 7 visit; X^1 = assessments to be performed at the Day 10 visit; X^2 = assessments to be performed at the Day 14 visit.

mm Maternal medical history for Hepatitis B and C will be obtained in lieu of laboratory testing.

nn Any adverse event or test showing abnormal results that is believed to be possibly/probably related to study drug treatment will be re-evaluated weekly (or as often as deemed prudent by the investigator) until the abnormality is resolved, returns to baseline, or is otherwise explained.

oo For study visits that are divided into multiple visits, adverse events and concomitant medications will be assessed at every visit.

pp Vital signs include blood pressure, temperature, heart rate, and respiration rate.

qq Perform complete physical examinations at Screening, Baseline, Weeks 24, 48 and ESDD visits.

rr For subjects ≥ 1 year of age, obtain measurements at **Screening, Baseline, Weeks 12, 24, and 48 only.** For subjects < 1 year of age, obtain measurements at Screening, Baseline, and all visits Weeks 4 through 48.

ss In the extension phase of the study, Tanner Stage assessments (Appendix 6) will be performed for subjects ≥ 6 years of age at the time of the visit, every 48 weeks, until subjects reach Tanner Stage 5, after which point Tanner assessments will no longer be performed.

tt Genotypic analysis for reverse transcriptase, protease, and integrase resistance will be done at screening for subjects with HIV-1 RNA >1,000 copies/mL. The investigator must have received the results from the screening genotype before proceeding with the Baseline visit. Historical genotypes should be obtained for subjects with HIV-1 RNA <50 copies/mL at screening.

uu CBC with differential and platelet count.

vv Chemistry profile: Albumin, alkaline phosphatase, AST, ALT, direct bilirubin, total bilirubin, bicarbonate, BUN, calcium, chloride, CPK, creatinine, magnesium, phosphorus, potassium, total protein, sodium, uric acid, amylase and lipase

ww Fasting glucose and lipid panel (total cholesterol, HDL, direct LDL, and triglycerides) metabolic assessments will be performed for subjects failing a current antiretroviral regimen (HIV-1 RNA >1,000 copies/mL) at screening and weighing ≥13 kg at the time of the visit, for the following visits: at Baseline, Weeks 24, 48, ESDD, and every 48 weeks in the extension phase of the study. 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.

xx Plasma storage samples banked for possible future protocol-related testing (virology, PK analysis) at post-Week 48 visits.

yy eGFR using Schwartz Formula (mL/min/1.73m^2) = k × L/Scr [(k is a proportionality constant, refer to Section 4.2 for details); L is height in centimeters (cm); and Scr is serum creatinine (mg/dL)]

zz Urine storage samples banked for possible future protocol-related testing (Urine chemistry including urine phosphorus and urine creatinine)

aaa Females of childbearing potential only.

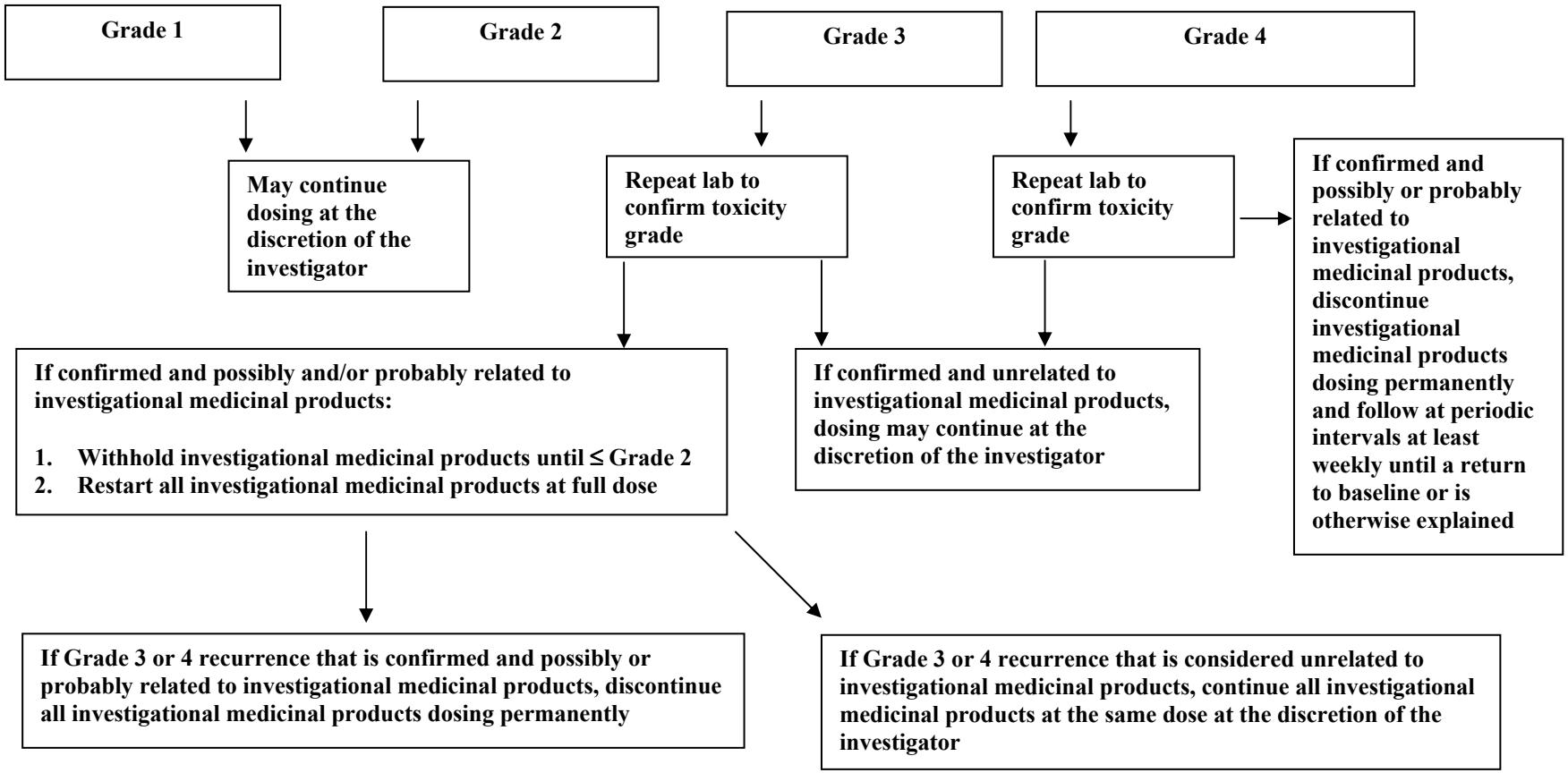
bbb Palatability of EVG suspension formulation will be assessed at Baseline/Day 1, Day 10 (**Part A only**), Week 24, and Week 48, as applicable.

ccc A trough (20 to 24 hours postdose) plasma PK sample will be collected. Subjects must come into the clinic without taking their dose of EVG and the PI/r and other BR components.

ddd Intensive PK sampling will be performed on Day 10 and **only applicable for subjects in Part A**. Subjects must come into the clinic without taking their dose of EVG and the PI/r and other BR components. PK samples will be collected at 0 (predose, ≤ 30 minutes), 3, 3.5, 5, and 8 hours postdose. Please refer to the PK manual for details.

eee All subjects will be given their dose of EVG + PI/r and other BR components with food in the clinic at Baseline, Day 10, Weeks 16 and 40.

Appendix 4. Management of Clinical and Laboratory Adverse Events



Appendix 5. GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

Version: 18 June 2012

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin HIV POSITIVE **Adult and Pediatric ≥ 57 Days**	8.5 to 10.0 g/dL 85 to 100 g/L	7.5 to < 8.5 g/dL 75 to < 85 g/L	6.5 to < 7.5 g/dL 65 to < 75 g/L	< 6.5 g/dL < 65 g/L
HIV NEGATIVE **Adult and Pediatric ≥ 57 Days**	10.0 to 10.9 g/dL 100 to 109 g/L OR Any decrease from Baseline 2.5 to < 3.5 g/dL 25 to < 35 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L OR Any decrease from Baseline 3.5 to < 4.5 g/dL 35 to < 45 g/L	7.0 to < 9.0 g/dL 70 to < 90 g/L OR Any decrease from Baseline ≥ 4.5 g/dL ≥ 45 g/L	< 7.0 g/dL < 70 g/L
Infant, 36–56 Days (HIV POSITIVE OR NEGATIVE)	8.5 to 9.4 g/dL 85 to 94 g/L	7.0 to < 8.5 g/dL 70 to < 85 g/L	6.0 to < 7.0 g/dL 60 to < 70 g/L	< 6.0 g/dL < 60 g/L
Infant, 22–35 Days (HIV POSITIVE OR NEGATIVE)	9.5 to 10.5 g/dL 95 to 105 g/L	8.0 to < 9.5 g/dL 80 to < 95 g/L	7.0 to < 8.0 g/dL 70 to < 80 g/L	< 7.0 g/dL < 70 g/L
Infant, 1–21 Days (HIV POSITIVE OR NEGATIVE)	12.0 to 13.0 g/dL 120 to 130 g/L	10.0 to < 12.0 g/dL 100 to < 120 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L	< 9.0 g/dL < 90 g/L
Absolute Neutrophil Count (ANC) **Adult and Pediatric, > 7 Days**	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

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Infant, 2 – ≤ 7 Days	1250 to 1500/mm^3 1.25 to 1.50 GI/L	1000 to < 1250/mm^3 1.00 to < 1.25 GI/L	750 to < 1000/mm^3 0.75 to < 1.00 GI/L	< 750/mm^3 < 0.75 GI/L
Infant, 1 Day	4000 to 5000/mm^3 4.00 to 5.00 GI/L	3000 to < 4000/mm^3 3.00 to < 4.00 GI/L	1500 to < 3000/mm^3 1.50 to < 3.00 GI/L	< 1500/mm^3 < 1.50 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
WBCs	2000/mm^3 to 2500/mm^3	1,500 to < 2,000/mm^3	1000 to < 1,500/mm^3	< 1000/mm^3
	2.00 GI/L to 2.50 GI/L	1.50 to < 2.00 GI/L	1.00 to < 1.50 GI/L	< 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	— —	— —

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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%

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	146 to 150 mEq/L 146 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	3.0 to 3.4 mEq/L 3.0 to 3.4 mmol/L	2.5 to < 3.0 mEq/L 2.5 to < 3.0 mmol/L	2.0 to < 2.5 mEq/L 2.0 to < 2.5 mmol/L	< 2.0 mEq/L < 2.0 mmol/L
Hyperkalemia	5.6 to 6.0 mEq/L 5.6 to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
Hypoglycemia **Adult and Pediatric ≥ 1 Month**	55 to 64 mg/dL 3.03 to 3.58 mmol/L	40 to < 55 mg/dL 2.20 to < 3.03 mmol/L	30 to < 40 mg/dL 1.64 to < 2.20 mmol/L	< 30 mg/dL < 1.64 mmol/L
Infant, < 1 Month	50 to 54 mg/dL 2.8 to 3.0 mmol/L	40 to < 50 mg/dL 2.2 to < 2.8 mmol/L	30 to < 40 mg/dL 1.7 to < 2.2 mmol/L	< 30 mg/dL < 1.7 mmol/L
Hyperglycemia, Nonfasting	116 to 160 mg/dL 6.42 to 8.91 mmol/L	> 160 to 250 mg/dL > 8.91 to 13.90 mmol/L	> 250 to 500 mg/dL > 13.90 to 27.79 mmol/L	> 500 mg/dL > 27.79 mmol/L
Hyperglycemia, Fasting	110 to 125 mg/dL 6.08 to 6.96 mmol/L	>125 to 250 mg/dL >6.96 to 13.90 mmol/L	>250 to 500 mg/dL >13.90 to 27.79 mmol/L	>500 mg/dL >27.79 mmol/L
Hypocalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥ 7 Days**	7.8 to 8.4 mg/dL 1.94 to 2.10 mmol/L	7.0 to < 7.8 mg/dL 1.74 to < 1.94 mmol/L	6.1 to < 7.0 mg/dL 1.51 to < 1.74 mmol/L	< 6.1 mg/dL < 1.51 mmol/L
Infant, < 7 Days	6.5 to 7.5 mg/dL 1.61 to 1.88 mmol/L	6.0 to < 6.5 mg/dL 1.49 to < 1.61 mmol/L	5.5 to < 6.0 mg/dL 1.36 to < 1.49 mmol/L	< 5.5 mg/dL < 1.36 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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
Hypophosphatemia **Adult and Pediatric > 14 Years** **Pediatric 1 Year–14 Years** **Pediatric < 1 Year**	2.0 to < LLN mg/dL 0.63 to < LLN mmol/L 3.0 to 3.5 mg/dL 0.96 to 1.12 mmol/L 3.5 to 4.5 mg/dL 1.12 to 1.46 mmol/L	1.5 to < 2.0 mg/dL 0.47 to < 0.63 mmol/L 2.5 to < 3.0 mg/dL 0.80 to < 0.96 mmol/L 2.5 to < 3.5 mg/dL 0.80 to < 1.12 mmol/L	1.0 to < 1.5 mg/dL 0.31 to < 0.47 mmol/L 1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L 1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.0 mg/dL < 0.31 mmol/L < 1.5 mg/dL < 0.47 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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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	> 10.0 to 12.0 mg/dL	> 12.0 to 15.0 mg/dL	> 15.0 mg/dL
	>ULN to 597 µmol/L	> 597 to 716 µmol/L	> 716 to 895 µmol/L	> 895 µmol/L
Hypouricemia	1.5 mg/dL to < LLN 87 µmol/L to < LLN	1.0 to < 1.5 mg/dL 57 to < 87 µmol/L	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L
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
Bicarbonate	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
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)	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
Pediatric >2 to <18 years	110 to 130 mg/dL	>130 to 190 mg/dL	> 190 mg/dL	NA
	2.84 to 3.37 mmol/L	>3.37 to 4.92 mmol/L	>4.92 mmol/L	

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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

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

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	3.0 g/dL to < LLN 30 g/L to < LLN	2.0 to < 3.0 g/dL 20 to < 30 g/L	< 2.0 g/dL < 20 g/L	NA

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

Notes:

Toxicity grades for Quantitative and Dipstick Hematuria will be assigned by Covance Laboratory, however for other laboratories, toxicity grades will only be assigned to Dipstick Hematuria.

With the exception of lipid tests, any graded laboratory test with a result that is between the LLN and ULN should be assigned Grade 0.

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

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

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

RESPIRATORY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Bronchospasm (acute)	FEV1 or peak flow reduced to 70% to 80%	FEV1 or peak flow 50% to 69%	FEV1 or peak flow 25% to 49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or Respiratory Distress	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated
Pediatric < 14 Years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90% to 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated

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

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

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

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

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alteration in Personality-Behavior or in Mood (eg, agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (eg, suicidal/homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and Behavioral/Attentional Disturbance (including dementia and ADD)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions
Cognitive and Behavioral/Attentional Disturbance (including dementia and Attention Deficit Disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
CNS Ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Developmental delay – **Pediatric ≤ 16 Years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than ER visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social/functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular Weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle 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

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Seizure: (new onset)	NA	1 seizure	2–4 seizures	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)
Seizure: (pre-existing) For Worsening of Existing Epilepsy the Grades Should Be Based on an Increase from Previous Level of Control to Any of These Levels	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR infrequent breakthrough seizures while on stable meds in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (eg, severity or focality)	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)
Seizure **– Pediatric < 18 Years**	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5–20 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting > 20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions

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

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

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

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

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

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

Basic Self-care Functions: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Usual Social & Functional Activities: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Appendix 6. Tanner Stages

1. Pubic hair (male and female)	
Tanner I	no pubic hair at all (prepubertal Dominic state)
Tanner II	small amount of long, downy hair with slight pigmentation at the base of the penis and scrotum (males) or on the labia majora (females)
Tanner III	hair becomes more coarse and curly, and begins to extend laterally
Tanner IV	adult-like hair quality, extending across pubis but sparing medial thighs
Tanner V	hair extends to medial surface of the thighs
2. Genitals (male) (One standard deviation around mean age)	
Tanner I	Testes, scrotum, and penis about same size and proportion as in early childhood
Tanner II	Enlargement of scrotum and testes; skin of scrotum reddens and changes in texture; little or no enlargement of penis (10.5-12.5)
Tanner III	Enlargement of penis, first mainly in length; further growth of testes and scrotum (11.5-14)
Tanner IV	Increased size of penis with growth in breadth and development of glans; further enlargement of testes and scrotum and increased darkening of scrotal skin (13.5-15)
Tanner V	Genitalia adult in size and shape
3. Breasts (female)	
Tanner I	no glandular tissue: areola follows the skin contours of the chest
Tanner II	breast bud forms, with small area of surrounding glandular tissue; areola begins to widen
Tanner III	breast begins to become more elevated, and extends beyond the borders of the areola, which continues to widen but remains in contour with surrounding breast
Tanner IV	increased breast size and elevation; areola and papilla form a secondary mound projecting from the contour of the surrounding breast
Tanner V	breast reaches final adult size; areola returns to contour of the surrounding breast, with a projecting central papilla.

Appendix 7. Definitions of HIV-1 Related Disease (adapted from CDC Guidelines)

Category B: Symptomatic Conditions in HIV-Infected Subjects

1. Bacillary angiomatosis
2. Candidiasis, oropharyngeal (thrush)
3. Candidiasis, vulvovaginal; persistent, frequent, or poorly responsive to therapy
4. Cervical dysplasia (moderate or severe)/cervical carcinoma in situ
5. Constitutional symptoms, such as fever (38.5°C) or diarrhea lasting > 1 month
6. Hairy leukoplakia, oral
7. Herpes zoster (shingles), involving at least two distinct episodes or more than one Dermatome
8. Idiopathic thrombocytopenic purpura
9. Listeriosis
10. Pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess
11. Peripheral neuropathy

Category C: AIDS-Defining Diagnoses

12. Candidiasis of bronchi, trachea, or lungs
13. Candidiasis, esophageal
14. Cervical cancer, invasive
15. Coccidioidomycosis, disseminated or extrapulmonary
16. Cryptococcosis, extrapulmonary
17. Cryptosporidiosis, chronic intestinal (> 1 month duration)
18. Cytomegalovirus disease (other than liver, spleen or nodes)
19. Cytomegalovirus retinitis (with loss of vision)
20. Encephalopathy, HIV-related

21. Herpes simplex: chronic ulcer(s) (> 1 month duration); or bronchitis, pneumonitis or esophagitis

22. Histoplasmosis, disseminated or extrapulmonary

23. Isosporiasis, chronic intestinal (> 1 month duration)

24. Kaposi's sarcoma

25. Lymphoma, Burkitt's (or equivalent term)

26. Lymphoma, immunoblastic (or equivalent term)

27. Lymphoma, primary, of brain

28. *Mycobacterium avium* complex or *Myobacterium kansasii*, disseminated or extrapulmonary

29. *Mycobacterium tuberculosis ,* pulmonary or extrapulmonary

30. *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary

31. Pneumocystis jirovecii pneumonia

32. Pneumonia, recurrent

33. Progressive multifocal leukoencephalopathy

34. *Salmonella* septicemia, recurrent

35. Toxoplasmosis of brain

36. Wasting syndrome attributed to HIV infection

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