CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2/3, Open-Label, Multi-Cohort Switch Study to Evaluate Emtricitabine/Tenofovir Alafenamide (F/TAF) in HIV-1 Infected Children and Adolescents Virologically Suppressed on a 2-NRTI-Containing Regimen	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404	
IND Number:	111851	
EudraCT Number:	2015-001339-19	
Clinical Trials.gov Identifier:	NCT02285114	
Indication:	HIV-1	
Protocol ID:	GS-US-311-1269	
Gilead Clinical Program Manager:	Name: Telephone: Fax:	PPD PPD PPD
Gilead Medical Monitor:	Name: Telephone: Fax:	PPD PPD PPD
Clinical Study Director:	Name: Telephone: Mobile: Fax:	PPD PPD PPD PPD
Protocol Version/Date:	Original: Amendment 1: Amendment 1.1 (South Africa): Amendment 2:	23 June 2014 20 November 2014 04 March 2015 02 August 2017

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PROTOCOL SYNOPSIS

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

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IND Number:	111851
EudraCT Number:	2015-001339-19
Clinical Trials.gov Identifier:	NCT02285114
Study Centers Planned:	Approximately 25 centers globally.
Objectives:	The primary objectives of this study are: • To evaluate the pharmacokinetics (PK) of tenofovir alafenamide (TAF) and confirm the TAF dose in HIV-1 infected children and adolescents virologically suppressed on a 2-NRTI-containing regimen • To evaluate the safety and tolerability of emtricitabine/tenofovir alafenamide (F/TAF) through Week 24 The secondary objectives of this study are: • To evaluate the PK of tenofovir (TFV) and emtricitabine (FTC) • To evaluate the safety, tolerability, and efficacy of F/TAF through Week 48
Study Design:	Open-label, multi-cohort switch study to evaluate the PK, safety, and efficacy of F/TAF in HIV-1 infected children (1 month to < 12 years) and adolescents (12 to <18 years) who are virologically suppressed (HIV-1 RNA < 50 copies/mL for at least 6 consecutive months) on a stable 2-NRTI-containing regimen. A minimum of 100 subjects aged 1 month to < 18 years of either sex will be enrolled as follows: **Cohort 1 (adolescents 12 to < 18 years, ≥ 35 kg):** All subjects in Cohort 1 (n = 25) will switch their current 2-NRTI-containing regimen to F/TAF while continuing their 3rd antiretroviral (ARV) agent through 48 weeks.

An intensive PK (IPK) evaluation will be conducted at the Week 2 visit. TAF dose confirmation will be established if the exposure is comparable to that associated with efficacy in adults.

All subjects in Cohort 1 will continue to receive F/TAF plus their 3rd ARV agent and return for study visits through Week 48.

Cohorts 2, 3, and 4

Cohorts 2, 3, and 4 will be enrolled by cohort into two parts (Parts A and B). Cohort 2 consists of 2 groups: Group 1 weighing ≥ 25 kg and Group 2 weighing 17 kg to < 25 kg.

All subjects in Cohort 2 Group 1 must be on a boosted protease inhibitor (PI) as their 3rd ARV agent and will switch their current 2-NRTI-containing regimen to open-label F/TAF while continuing their boosted PI through 48 weeks.

All subjects in Cohort 2, Group 2 and Cohorts 3 and 4 will be on a boosted PI or other protocol-specified 3rd agents and will switch their current 2-NRTI-containing regimen to open-label F/TAF while continuing their 3rd agents through 48 weeks.

A minimum of 10 subjects who are on boosted-ATV as their 3rd ARV agent will be enrolled into Part A of each group of Cohort 2, as well as Cohorts 3 and 4.

Cohorts 2, 3, and 4 will be enrolled as follows:

Part A

Cohort	Age Range	Weight Range	Number of Subjects		
			ATV + F/TAF	LPV or DRV + F/TAF	Other 3rd ARV Agents + F/TAF
2, Group 1	6 to < 12 years	≥ 25 kg	n ≥ 10	n ≥ 6	n/a
2, Group 2 (subjects able to swallow a tablet)	2 to < 12 years	17 kg to < 25 kg	n ≥ 10	n ≥ 7	
3[b] (subjects unable to swallow a tablet)	2 to < 6 years	TBD	n ≥ 10	n ≥ 7	
4[a,b]	1 month to < 2 years	TBD	n ≥ 10	n ≥ 7	

a DRV is not approved for Cohort 4
b Formulation, dosing, and population specific details for Cohorts 3 and 4 will be added via a protocol amendment after data is obtained from Cohort 2.

All subjects in Part A will undergo an IPK evaluation at either the Week 2 or Week 4 visit (+7 days) to confirm the dose of TAF.

Part B

Screening will be initiated for Part B following confirmation of TAF dose in Part A for each group of Cohort 2 and Cohorts 3 and 4. Approximately 10 additional total subjects will be enrolled in Part B and will receive F/TAF while continuing their 3rd ARV agent through 48 weeks.

Number of Subjects Planned: A minimum of 100 subjects will be enrolled.

Target Population: HIV-1 infected adolescents and children who have been virologically suppressed for ≥ 6 consecutive months prior to screening on a stable 2-NRTI-containing regimen.

Duration of Treatment: Subjects will receive study treatment for at least 48 weeks.

CCI [redacted]

Diagnosis and Main Eligibility Criteria: HIV-1 infected pediatric patients at Baseline/Day 1.

Currently on a stable 2-NRTI-containing regimen that includes a 3rd ARV agent for ≥ 6 consecutive months prior to screening.

Body weight and age at screening for all cohorts is as follows:

Cohort	Age Range	Weight
1	12 years to < 18 years	≥ 35 kg
2 (Group 1)	6 years to < 12 years	≥ 25 kg
2 (Group 2) (subjects able to swallow a tablet)	2 years to < 12 years	17 kg to < 25 kg
3 (subjects unable to swallow a tablet)	2 years to < 6 years	TBD[a]
4	1 month to < 2 years	TBD[b]

a Body weight cutoff at screening to be determined based upon analysis of short-term safety and PK data from Cohort 2 Part A before initiating Cohort 3 Part A

b Body weight cutoff at screening to be determined based upon analysis of short-term safety and PK data from Cohort 2 Part A & Cohort 3 Part A

No documented or suspected resistance to TFV or FTC, including, but not limited to, the presence of reverse transcriptase mutations K65R, K70E, M184V/I, or 3 or more thymidine analog-associated mutations (TAMs) that include M41L or L210W (TAMs are M41L, D67N, K70R, L210W, T215Y/F, K219Q/E/N/R).

No laboratory evidence of current active HBV or HCV infection.

Plasma HIV-1 RNA levels < 50 copies/mL for ≥ 6 consecutive months.

Estimated glomerular filtration rate (eGFR) ≥ 90 mL/min/1.73 m^2 by (Schwartz) formula.

Study Procedures/ Frequency:

At the Screening, Baseline/Day 1, and all subsequent study visits, laboratory analyses (hematology, chemistry, and urinalysis), HIV-1 RNA, CD4+ cell count, complete or symptom directed physical examinations, and eGFR using the Schwartz formula will be performed. Serum (screening) or urine (all other visits) pregnancy tests will be performed on female subjects of childbearing potential.

At screening, HBV and HCV serology will be analyzed.

Subjects will return for study visits at Weeks 1, 2, 4, 8, 12, 24, 36, and 48. CCI [redacted]

Adverse events and concomitant medications will be assessed at each visit.

Serum will be collected for bone safety tests (collected fasted):

- Cohort 1 only: Baseline/Day 1, Weeks 4, 12, 24, and 48 CCI [redacted]
- Cohorts 2, 3, and 4: Baseline/Day 1, Weeks 8, 12, 24, 48, CCI [redacted]

For all Cohorts, urine will be collected for urine chemistry and selected renal safety tests, including retinol binding protein and beta-2-microglobulin, at Baseline/Day 1, Weeks 2, 4, 8, 12, 24, 48[redacted]

For Cohorts 1 and 2 (all groups), metabolic assessments will be collected for fasting glucose and lipid panel (total cholesterol, HDL, direct LDL, and triglycerides) at Baseline/Day 1, Weeks 24, 48, CCI [redacted]. The fasting requirement for Cohorts 3 and 4 will be specified in a future protocol amendment.

Tanner stage assessment (Appendix 7) will be performed for subjects ≥ 6 years of age at the time of the visit at Baseline/Day 1, Weeks 24, 48, CCI [redacted] or until subjects reach Tanner Stage 5, after which point Tanner assessments will no longer be performed.

For all Cohorts, dual energy x-ray absorptiometry (DXA) scans of the lumbar spine and total body will be performed at Baseline/Day 1, Weeks 24, 48, CCI [redacted] to measure spine bone mineral density (BMD) and total body BMD.

PK sampling:

Single PK samples will be collected at the following visits for all cohorts:

- Weeks 1 and 24: a single random PK sample.
- Weeks 4 and 12: a single observed dosing PK sample at any time between 15 min to 4 hours post dose. (Note: Single observed dosing PK sample does not need to be collected at Week 4 if Intensive PK is also collected at the Week 4 visit)
- Week 8: a trough sample at 0 hours (pre-dose, ≤ 30 minutes prior to dosing) at Week 8.

Intensive PK sampling:

- Cohort 1 will participate in an Intensive PK (IPK) evaluation at the Week 2 visit as detailed in the PK manual.
- Cohort 2 Part A will participate in an IPK evaluation during either the Week 2 or Week 4 visit or within 7 days after the completion of Week 2 or Week 4 visit as detailed in the PK manual. The IPK collection schedule and fasting requirement for Cohorts 3 and 4 will be specified in a future protocol amendment.

PBMC collection:

- PBMC collection will be performed at study sites that can perform PBMC processing.
- Cohorts 1 and 2: PBMC collection will be performed at the Week 8 visit.
- Cohort 3, and 4: PBMC collection schedule will be specified in a future protocol amendment.

Palatability and Acceptability Assessment:

- Cohort 1: At the Week 2 visit, palatability and acceptability will be assessed 30 - 60 minutes after study drug dosing for all subjects undergoing IPK sampling. Acceptability will also be assessed 30 - 60 minutes after study drug dosing for active subjects at the next study visit immediately following approval of this protocol at the site.
- Cohort 2 Part A: Palatability and acceptability will be assessed at the Week 2 or Week 4 visit, or within 7 days after the completion of the Week 2 or Week 4 visit, 30 - 60 minutes after study drug dosing for all subjects undergoing IPK sampling.
- Cohorts 3 and 4 Part A: Palatability and acceptability will be assessed for subjects undergoing IPK sampling. Assessment schedule will be specified in a future protocol amendment.

Subjects who prematurely discontinue from the study CCI [redacted] will be required to return to the clinic for a 30-Day Follow-up Visit.

Test Product, Dose, and Mode of Administration:

F/TAF tablets administered orally QD in combination with a 3rd ARV agent, with or without food (as determined by the 3rd ARV agent), dosed as follows:

Cohort	Age and body weight	F/TAF dose (mg) with 3rd agent
1	12 to <18 years, ≥ 35 kg	200/25 for unboosted 3rd agent 200/10 for boosted 3rd agent
2, Group 1	6 to < 12 years, ≥ 25 kg	200/25
2, Group 2 (subjects able to swallow a tablet)	2 to < 12 years, ≥ 17 to < 25 kg	120/15
3 (subjects unable to swallow a tablet)	2 to < 6 years, TBD	TBD[a]
4	1 month to < 2 years, TBD	TBD[a]

a Dose, formulation, and population specific details will be specified by protocol amendment after clinical safety, efficacy, and PK data from Cohorts 1 and 2 are available to guide dose and formulation selection of F/TAF to be administered in Cohorts 3 and 4.

Criteria for Evaluation:

Safety:	Adverse events and clinical laboratory tests, including selected renal and bone safety tests and BMD (assessed by DXA)
Efficacy:	The efficacy endpoints are: • The percentage of subjects with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as defined by the US FDA-defined snapshot algorithm • The change from baseline in CD4+ cell count (cells/μL) and CD4+ percentage at Weeks 24 and 48
Pharmacokinetics:	The following plasma PK parameters will be calculated for TAF, TFV and FTC (as applicable): AUC_{tau}, AUC_{last}, C_{tau}, C_{max}, C_{last}, T_{max}, T_{last}, λ_z, apparent CL, apparent V_z, and $T_{½}$. CCI [redacted]
Statistical Methods:	Plasma concentration and parameters of TAF, TFV, and FTC will be summarized using descriptive statistics by cohort, dose level and type of boosted PI (eg, ATV/r or other PIs/r) if applicable. The AUC_{tau} of TAF obtained in subjects from Cohort 1 or Part A of Cohort 2 Groups 1 and 2, Cohort 3, and Cohort 4, respectively, will be compared to historical adult data (ie, Study GS-US-311-1089). The comparisons will be conducted within each cohort and by dose level (ie. 200/25 mg vs 200/10 mg), when applicable. TAF dose confirmation will be established if the lower bound of the 90% confidence interval (CI) of the geometric mean ratio (pediatric subjects vs adult subjects) is above 70% for TAF AUC_{tau}. The 95% CI of the geometric mean estimates of Cl/F and V_z /F will also be constructed for TAF. For efficacy and safety endpoints, results from each group or cohort will be descriptive in nature. F/TAF results from each cohort will also be combined to describe the overall efficacy and safety profile of F/TAF in pediatric subjects. The percentage of subjects with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as defined by the US FDA-defined snapshot algorithm will be summarized by group or cohort. The 95% CI for the point estimate for F/TAF will be constructed.

The change from baseline in CD4+ cell count and CD4+ percentage will be summarized by visit, group, and cohort using descriptive statistics.

CCI [redacted]

Bone and renal safety test data will be summarized by visit, group, and cohort. The incidences of treatment-emergent adverse events and treatment-emergent laboratory abnormalities will be summarized by group, cohort, and overall.

Cohort 1: Twenty-five subjects in Cohort 1 will provide at least 90% power to target a 95% confidence interval within 60% and 140% of the geometric mean estimate of apparent CL and apparent V_z of TAF, respectively, assuming a standard deviation of 0.60 for CL and 0.58 for V_z (natural log scale) estimated from Study GS-US-292-0106 Cohort 1 Part A.

Cohort 2 (Group 1) Part A: At least 10 subjects on boosted ATV + F/TAF and 6 subjects on boosted LPV or DRV + F/TAF, compared with the population PK data from 44 adult subjects on boosted ATV + F/TAF and 87 adult subjects on boosted LPV or DRV + F/TAF in Study GS-US-311-1089, respectively, will each provide at least 80% power to show the lower bound of a 90% CI of geometric mean ratio (pediatric subjects vs. adult subjects) greater than 70% for AUC_{tau} of TAF, assuming that the expected geometric mean ratios of TAF AUC_{tau} between pediatric subjects and adult subjects are equal to 1 and the standard deviations are 0.40 (with boosted ATV + F/TAF) and 0.33 (with boosted LPV or DRV + F/TAF) ng*hr/mL for TAF AUC_{tau} (natural log scale) estimated from the population PK data in Study GS-US-311-1089.

Cohorts 2 (Group 2), 3, and 4, Part A: At least 10 subjects on boosted ATV+F/TAF and at least 7 subjects on any other 3rd agent + F/TAF in each group or cohort, compared with the population PK data from 292 adult subjects on any 3rd agent + F/TAF in Study GS-US-311-1089, will provide 90% power to show the lower bound of a 90% CI of geometric mean ratio (pediatric subjects vs. adult subjects) greater than 70% for AUC_{tau} of TAF, assuming that the expected geometric mean ratio of TAF AUC_{tau} between pediatric subjects and adult subjects is equal to 1 and the standard deviation is 0.48 ng*hr/mL for TAF AUC_{tau} (natural log scale) estimated from the population PK data in Study GS-US-311-1089.

	A total of at least 100 subjects receiving F/TAF from Cohort 1, Parts A and B of Cohort 2 (Groups 1 and 2), Cohort 3, and Cohort 4 combined will provide reasonable assessment of safety through Week 48 in pediatric subjects.

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 Immune Deficiency Syndrome
AK	adenylate kinase
ALT	alanine aminotransferase
ARV	Antiretroviral
AST	aspartate aminotransferase
ATV/r	ritonavir boosted atazanavir
AUC	area under the plasma/serum/peripheral blood mononuclear cell concentration versus time curve
AUC_{tau}	area under the concentration verses time curve over the dosing interval
BsAP	Bone specific alkaline phosphatase
BMD	bone mineral density
BUN	blood urea nitrogen
CBC	complete blood count
C_{last}	the last observed quantifiable plasma concentration of drug
CL/F	the apparent oral clearance after administration of the drug: $CL/F = Dose/AUC_{inf}$ where “Dose” is the dose of the drug
C_{max}	the maximum observed serum/plasma/peripheral blood mononuclear (PBMC) concentration of drug
CNS	central nervous system
COBI, /co	cobicistat
C_{tau}	the observed drug concentration at the end of the dosing interval
CPK	creatine phosphokinase
CRF	case report form(s)
CRO	contract (or clinical) research organization
CSR	Clinical Study Report
CTX	type 1 collagen crosslinked C-telopeptide
DXA	Dual-energy X-ray absorptiometry
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DRV/r	ritonavir boosted darunavir
DSPH	Drug Safety and Public Health
DTG	Dolutegravir
D2000006	Gilead pre-clinical study: “A cardiovascular profile study following a single oral administration of GS-7340 in the unrestrained conscious beagle dog”
ECG	Electrocardiogram
EDC	electronic data capture

eCRF	electronic case report form(s)
eGFR	estimated glomerular filtration rate
EFV	Efavirenz
EVG	elvitegravir
E/C/F/TAF	elvitegravir (EVG) 150 mg/cobicistat (COBI) 150 mg/emtricitabine (FTC) 200 mg/tenofovir alafenamide (TAF) 10 mg single tablet regimen
ESDD	Early Study Drug Discontinuation
FAS	full analysis set
FDA	(United States) Food and Drug Administration
FDC	Fixed-Dose Combination
FTC	Emtricitabine
F/TAF	emtricitabine/tenofovir alafenamide
GCP	Good Clinical Practice (Guidelines)
GSI	Gilead Sciences, Inc.
GS-7340	tenofovir alafenamide, TAF, L-Alanine, N-[(S)-[[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]/ phenoxyphosphinyl]-, 1-methylethyl ester
HAART	highly active antiretroviral therapy
HBsAg	hepatitis B virus surface antigen serology
HBV	hepatitis B virus
HCV	hepatitis C virus
HCVAb	hepatitis C virus serology
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
HLGT	high-level group term
HLT	high-level term
HSP	Hysterosalpingogram
IB	investigator's brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Indpendent Ethics Committee
IND	Investigational New Drug (Application)
INSTI	integrase strand transfer inhibitor
IMP	Investigational Medicinal Product
IRB	institutional review board
IUD	intrauterine device
IWRS	interactive web response system
KS	Kaposi's sarcoma
LLN	lower limit of the normal range
LLOQ	lower limit of quantification

LLT	low-level term
LPV/r	ritonavir boosted lopinavir
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
mmHg	millimeters mercury
NNRTI	non-nucleoside reverse transcriptase inhibitor
NtRTI	nucleotide reverse transcriptase inhibitor
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
NVP	Nevirapine
P1NP	procollagen Type 1 N-terminal propeptide
PBMC	peripheral blood mononuclear cell
PC-120-2005	Gilead pre-clinical study: "Effect of GS-7340-03 on Cloned hERG Potassium Channels Expressed in Human Embryonic Kidney Cells"
PI	protease inhibitor
PK	Pharmacokinetic
PTH	parathyroid hormone
QD	once daily
R990186	Gilead pre-clinical study: "A pharmacologic assessment of the effect of GS-7340-02 on the renal system of the rat"
R990187	Gilead pre-clinical study: "A pharmacologic assessment of the effect of GS-7340-02 on the gastrointestinal motility in the rat"
R990188	Gilead pre-clinical study: "A pharmacologic assessment of the effect of GS-7340-02 on the central nervous system of the rat"
RAL	Raltegravir
RBC	Red blood cells
RNA	ribonucleic acid
RPV	Rilpivirine
SAE	serious adverse event
SOC	system organ class
SOP	Standard Operating Procedure
STB	Stribild®, EVG/COBI/FTC/TDF (E/C/F/TDF) STR
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAF	tenofovir alafenamide (GS-7340)
TAF fumarate	tenofovir alafenamide fumarate (GS-7340-03)
TAM	thymidine analog-associated mutations
TBD	to be determined
TDF	tenofovir disoproxil fumarate
TFV	Tenofovir
TFV-DP	tenofovir diphosphate (TFVpp)
T_{max}	the time (observed time point) of Cmax

UGT	uridine glucuronosyltransferase
ULN	upper limit of the normal range
US	United States
V_z /F	apparent volume of distribution during the terminal phase
λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the serum, plasma concentration of drug versus time curve

1. INTRODUCTION

1.1. Background

Human immunodeficiency virus-1 (HIV-1) infection is a life-threatening and serious disease that is of major public health interest around the world. There are approximately 2.1 million people in North America and Western and Central Europe living with HIV-1 and 36.7 million people worldwide {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2016}, including 2.1 million children under 15 years of age {Joint United Nations Programme on HIV/AIDS (UNAIDS) 2016}. This figure is likely to underestimate the HIV disease burden in the pediatric population using the European Medicines Agency (EMA) categorization of adolescence as from 12 to 16 or 18 years, depending on the region (EMA, Note for Guidance CPMP/ICH/2711/99). The infection, if left untreated or suboptimally treated, is characterized by deterioration in immune function, 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 {Mocroft 1998, Palella 1998, Sterne 2005}.

Disease Pathophysiology

The pathogenesis of HIV-1 infection and the general virologic and immunologic principles underlying the use of ARV therapy are similar between HIV-1 infected adult and pediatric patients. However, there are some important and unique issues for HIV-1 infected infants, children, and adolescents, including the following {Panel on Antiretroviral Therapy and Medical Management of HIV-infected Children 2011}:

- Acquisition of infection through perinatal exposure for many infected children
- In utero, intrapartum, and/or postpartum neonatal exposure to zidovudine and other ARV medications in most perinatally infected children
- Age-specific differences in CD4+ cell counts and percentages
- Changes in pharmacokinetic parameters with age caused by the continuing development and maturation of organ systems involved in drug metabolism and clearance
- Differences in the clinical and virologic manifestations of perinatal HIV-1 infection secondary to the occurrence of primary infection in growing, immunologically immature persons
- Special considerations associated with adherence to ARV treatment for infants, children, and adolescents
- Need for longer duration of therapy, with potentially greater implications than in adults for long-term toxicity and development of resistance
- Differences in physiological development of certain body systems, including the skeletal system, where peak bone mass is not achieved until early adulthood

Additional issues that may need to be considered include the fact that the processes involved in growth and development during childhood and adolescence can affect the adverse event profile of drugs, and that developmental changes associated with aging and growth are often not linear {Ginsberg 2004, McCarver 2004}.

Treatment

The goal of ARV therapy for HIV-1 infection is to delay disease progression, improve immune function, and increase the duration of survival by achieving maximal and prolonged suppression of HIV-1 replication. The availability of highly active antiretroviral therapy (HAART) combinations for the treatment of HIV-1 infection has resulted in a dramatic reduction in Acquired Immunodeficiency Syndrome (AIDS) related morbidity and mortality in the US and Europe {Mocroft 1998, Palella 1998, Sterne 2005}. However, eradication of the virus is not possible with therapies that are currently available. These therapies have several distinct adverse events such as mitochondrial dysfunction, metabolic abnormalities, hematologic toxicities, and allergic reactions.

The 2017 Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection generally recommend the use of 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) in combination with a 3rd agent (a non-nucleoside reverse transcriptase inhibitor [NNRTI], a boosted protease inhibitor [PI] or an integrase strand transfer inhibitor [INSTI]) for treatment of children and adolescents with HIV infection. The choice of a regimen, including the 3rd agent, is individualized based on a number of factors including characteristics of the proposed regimen, patient characteristics and results of resistance testing {HHS Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children with HIV 2017, Welch 2009}.

Tenofovir (TFV) is a nucleotide analog that inhibits HIV-1 reverse transcription. While tenofovir disoproxil fumarate (TDF), an oral prodrug of TFV, is a preferred NtRTI for initial therapy, nephrotoxicity is an identified risk, and reductions in bone mineral density (BMD) have been shown that are larger than those seen with other NRTIs. Tenofovir alafenamide (TAF) is also an oral prodrug of TFV. TAF is more stable in plasma than TDF, provides higher intracellular levels of the active phosphorylated metabolite tenofovir diphosphate (TFV-DP), and approximately 90% lower circulating levels of TFV relative to TDF at the clinical doses. The distinct metabolism of TAF offers the potential for an improved clinical profile compared with TDF. TAF is coformulated with the integrase strand transfer inhibitor elvitegravir (EVG), cobicistat (COBI), and emtricitabine (FTC) as Genvoya® (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide [E/C/F/TAF]) and with FTC as Descovy® (emtricitabine/tenofovir alafenamide [F/TAF]). The fixed-dose combination (FDC) Genvoya® has been approved by the FDA and EMA for the treatment of HIV infection in ARV-naive individuals aged ≥ 12 years with estimated creatinine clearance ≥30 mL/min. The FDC Descovy® has also been approved in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older weighing at least 35 kg.

Development of F/TAF increases the options available for the construction of ARV regimens for HIV-1 infected pediatric patients, and simplifies dosing of the NRTI/NtRTI backbone. The small F/TAF tablet size due to the low predicted mg dose of TAF in combination with FTC should improve acceptability for children who can swallow tablets.

1.2. Tenofovir Alafenamide (TAF, GS-7340)

1.2.1. General Information

Tenofovir alafenamide (GS-7340, TAF, or L-Alanine, N-[(S)-[[(1R)-2-(6-amino-9H-purin-9-yl)-1-methylethoxy]methyl]/phenoxyphosphinyl]-, 1-methylethyl ester) is a second generation oral prodrug of TFV, a nucleotide analog that inhibits HIV-1 reverse transcription. Tenofovir is metabolized intracellularly to the active metabolite, TFV-DP, a competitive inhibitor of HIV-1 reverse transcriptase (RT) that terminates the elongation of the viral DNA chain.
The intracellular metabolism of TAF and TFV are consistent with the 600-fold enhancement in anti-HIV activity in cell culture of TAF over TFV.

TAF has been evaluated in a broad range of patients (e.g. treatment-naïve, virologically suppressed, etc) as part of Genvoya® (E/C/F/TAF), Descovy® (F/TAF), or Odefsey® (rilpivirine/emtricitabine/tenofovir alafenamide [F/R/TAF]). Specifically, Study GS-US-292-0106 evaluated E/C/F/TAF (adult dose) in treatment-naïve adolescents. The conclusions for Cohort 1 (ART-naive adolescents treated with E/C/F/TAF) in this study are as follows:

- High virologic success was achieved (as assessed using the FDA-defined snapshot algorithm with HIV-1 RNA < 50 copies/mL) in ART-naive adolescents (90.0% and 92.0% virologic success at Weeks 24 and 48, respectively), demonstrating efficacy of the E/C/F/TAF FDC in this age group. These results are in accordance with pharmacokinetic (PK) data (presented in an earlier CSR) that confirmed the E/C/F/TAF 150/150/200/10 mg doses for each component.

- There was evidence of a robust immunological response to E/C/F/TAF in ART-naive adolescents. The mean (SD) increase from baseline in CD4 cell count was 191 (175.2) cells/µL at Week 24 and 224 (170.3) cells/µL at Week 48. The mean (SD) increase from baseline in CD4% was 7.7% (4.77%) at Week 24 and 9.3% (5.19%) at Week 48.

- E/C/F/TAF was well tolerated, as evidenced by the low incidence of study-drug-related SAEs and the absence of AEs leading to discontinuation of study drug.

- The lack of notable changes from baseline in height-age spine and TBLH BMD Z-scores at Weeks 24 and 48 indicates that subjects mineralized bone at rates consistent with those of the reference population. Few subjects experienced a clinically relevant decrease from baseline in BMD.

- Changes from baseline in serum creatinine and eGFR were consistent with the inhibitory effect of COBI on renal tubular secretion of creatinine, and are not considered reflective of changes in actual glomerular filtration. There were decreases from baseline in proteinuria, as assessed by UPCR (urine protein to creatinine ratio).

- E/C/F/TAF has been approved in adults and pediatric patients 12 years of age and older in the US and EU {Gilead Sciences Inc 2016, Gilead Sciences International Limited 2016}.

Please refer to the respective Investigator's Brochure for further information, including data from adult studies.

1.2.2. Preclinical Pharmacology and Toxicology

1.2.2.1. Primary Pharmacodynamics

TAF, like TDF, is an orally bioavailable prodrug of TFV. Following oral administration, TAF is metabolized to TFV, a nucleotide analog (i.e., a nucleoside monophosphate analog) which is not dependent on an intracellular nucleoside kinase activity for the first step in the conversion to the active metabolite, TFV-DP. The cellular enzymes responsible for TFV metabolism to the active diphosphorylated form are adenylate kinase (AK) {Robbins 1995} and nucleotide diphosphate kinase, which are highly active and ubiquitous. AK exists as multiple isozymes (AK1 to AK4), with the phosphorylation of TFV mediated most efficiently by AK2.

The intracellular metabolism of TAF and TFV are consistent with the 600-fold enhancement in anti-HIV activity in cell culture of TAF over TFV. Metabolism of TAF was also studied in different human blood lymphocyte subpopulations, CD4+ and CD8+ T-cells, NK cells, B-cells and macrophages/monocytes. TAF is metabolized inside host cells to the active metabolite TFV-DP. Concentration of the active metabolite TFV-DP was substantial in all cell populations.

1.2.2.2. Safety Pharmacology

TAF monofumarate (GS-7430-02) has been evaluated to determine potential effects on the central nervous system (Study R990188), renal system (Study R990186), cardiovascular system (Study D2000006) and gastrointestinal systems (Study R990187). Single doses did not induce pharmacologic effects on the central nervous system of the rat (1000 mg/kg), the renal system of the rat (1000 mg/kg), or the cardiovascular system of the dog (100 mg/kg). TAF monofumarate (at 1000 mg/kg) reduced distal transit and increased stomach weights starting 2 hours postdosing with reversibility beginning by 6 hours after dosing. The NOEL for gastrointestinal motility was 100 mg/kg. The IC_{50} for the inhibitory effect of TAF fumarate (GS-7340-03) on hERG potassium current was estimated to be greater than 10 μM (Study PC-120-2005).

1.2.3. Nonclinical Pharmacokinetics

Information regarding the TAF nonclinical PK is available in the current F/TAF IB.

1.2.4. Clinical Trials of Single Agent Tenofovir Alafenamide (TAF, GS-7340) or Fixed-Dose Combination (FDC) emtricitabine/tenofovir alafenamide (F/TAF)

Clinical trials entailing the use of TAF or F/TAF FDC are included in the F/TAF IB.

Drug Interaction Studies with TAF and 3rd ARV Agents

TAF systemic exposure was found to be increased by COBI via P-glycoprotein inhibition. This led to the selection of TAF 10 mg in the E/C/F/TAF FDC tablet, which achieved TAF exposure bioequivalent to that achieved with TAF 25 mg (Study GS-US-292-0103), which is considered the reference exposure.

Three drug-drug interaction studies (GS-US-311-0101, GS-US-120-0117, and GS-US-120-0118) have been conducted to determine the drug interaction potential of commonly used 3rd agents with TAF. In combination, Studies GS-US-311-0101, GS-US-120-0117, and GS-US-120-0118 provide drug interaction data between TAF and boosted protease inhibitors (DRV/r, ATV/r, LPV/r), non-nucleoside reverse transcriptase inhibitors (EFV and RPV), and the integrase strand transfer (INSTI) inhibitor dolutegravir (DTG), and the effect of these 3rd agents on TAF exposure is shown in Table 1-1.

While no clinical drug-drug interaction studies of TAF were conducted with RAL, MVC and NVP, no clinically relevant drug-drug interaction is expected based upon preclinical and clinical information.

Table 1-1. TAF AUC upon Co-administration of TAF (10 or 25 mg) with 3rd Agent in Adults

Study	Co-administered 3rd agent	TAF dose evaluated in the DDI study (mg)	Effect of 3rd agent on TAF AUC_{last}
GS-US-120-0118	ATV/r	10	↑ 91%
	LPV/r	10	↑47%
	DRV/r	10	↑ 6%
	DTG	10	↑19%
GS-US-120-0117	RPV	25	↓ 4%
GS-US-311-0101	EFV	40	↓ 14%

Study GS-US-311-1089 is an ongoing 48-week, randomized, double-blinded, switch study to evaluate F/TAF in HIV-1 infected, virologically suppressed adults on regimens containing FTC/TDF. Safety and efficacy of F/TAF 200/10 or 200/25 mg in combination with the appropriate 3rd agent is being evaluated in addition to TAF and TFV PK.

1.3. Emtricitabine (FTC, Emtriva®)

Emtricitabine (5-fluoro-1-[(2R, 5S)-2-(hydroxymethyl)-[1, 3]-oxathiolan-5-yl] cytosine, FTC) is an NRTI that has demonstrated potent and selective inhibition of HIV. In HIV-infected adults, FTC is administered as a 200 mg QD dose concurrently with other ARV drugs. The 200 mg FTC capsule formulation was approved by the US Food and Drug Administration (FDA) for marketing on 02 July 2003 and is available under the name Emtriva®. In the European Union (EU), marketing authorization was granted for both the 200 mg Emtriva® capsule formulation and a 10 mg/mL Emtriva® oral solution formulation on 24 October 2003, with indications for the treatment of HIV infection concurrently with other antiretroviral drugs in both adult and pediatric patients. Further information is available in the current Prescribing Information for Emtriva®.

1.4. Rationale for This Study

The success of HAART and the apparent benefits of maximally suppressed viremia have shifted clinical attention towards ARV agents that optimize long-term safety and tolerability. Young, newly infected patients are diagnosed earlier, initiate therapy earlier and look ahead towards lifelong therapy {Prejean 2011}. Renal and bone health, in both of these contexts are increasingly important {Capeau 2011}

Although more than 20 different ARV agents in five classes are available for the treatment of HIV infection in adults, adolescents have limited treatment options for effective, safe and well tolerated once daily therapy. Adolescents with HIV infection are in need of ARV regimens for which therapeutic dosing has been validated by pharmacokinetic data. Many adolescents with HIV infection would benefit from the availability of a simplified, fixed dose combination of F/TAF that combines potent efficacy, tolerability, a favorable toxicity profile, and practical, convenient dosing.

Gilead has developed the FDC product F/TAF. Children ages 2 to < 12 years old will benefit from the availability of an NRTI/NtRTI backbone in a single formulation to be administered with other ARV agents.

Switching from a 2-NRTI-containing ARV regimen to a TAF-containing ARV regimen may lead to improvement in renal and bone safety parameters due to lower plasma TFV exposure.

HIV-infected pediatric subjects may benefit from a fixed dose tablet or age appropriate formulation of F/TAF, which has the potential for an improved renal and bone safety profile relative to TDF, an important consideration for a population in which peak bone mass has not yet been achieved and for whom HIV treatment is anticipated to be life-long.

1.5. Rationale for Dose Selection

The proposed F/TAF doses for this study are expected to provide plasma exposures in the pediatric population that are comparable to those associated with safety and efficacy in adults.

1.5.1. F/TAF Dose in Adolescents 12 to < 18 years of Age Weighing ≥ 35 kg

The recommended F/TAF dose in adolescents 12 to < 18 years is 200/10 mg or 200/25 mg based on the coadministered 3rd agent. Exposures of TAF, TAF-metabolite TFV, and FTC observed following administration of F/TAF 200/10 mg or 200/25 mg in adolescents are consistent with exposures observed in adults.

For boosted regimens, such as LPV/r, DRV/r and ATV/r, the recommended F/TAF dose is the adult strength tablet, 200/10 mg. For unboosted regimens, such as EFV, NVP, RAL and DTG, the recommended F/TAF dose is the adult strength tablet, 200/25 mg.

1.5.2. F/TAF Dose in Children 6 to < 12 Years of Age Weighing ≥ 25 kg and 2 to < 12 Years of Age Weighing 17 to < 25 kg

In the US, F/TAF 200/25 mg is approved for use in adults and adolescents (greater than 12 years of age and weighing ≥ 35 kg) when used with unboosted or boosted 3rd agents.

For children 6 to < 12 years old weighing ≥ 25 kg, the proposed F/TAF dose for evaluation is 200/25 mg (Table 1-2).

For children 2 to < 12 years old weighing 17 to < 25 kg, a reduced F/TAF dose of 120/15 mg is proposed for evaluation (Table 1-2).

Table 1-2. Pediatric F/TAF Dosing and Tablet Strength by Body Weight

Weight Band in (kg)	Strength F/TAF[a] (mg)
≥ 25 to < 35	200/25[b]
≥ 17 to < 25	120/15

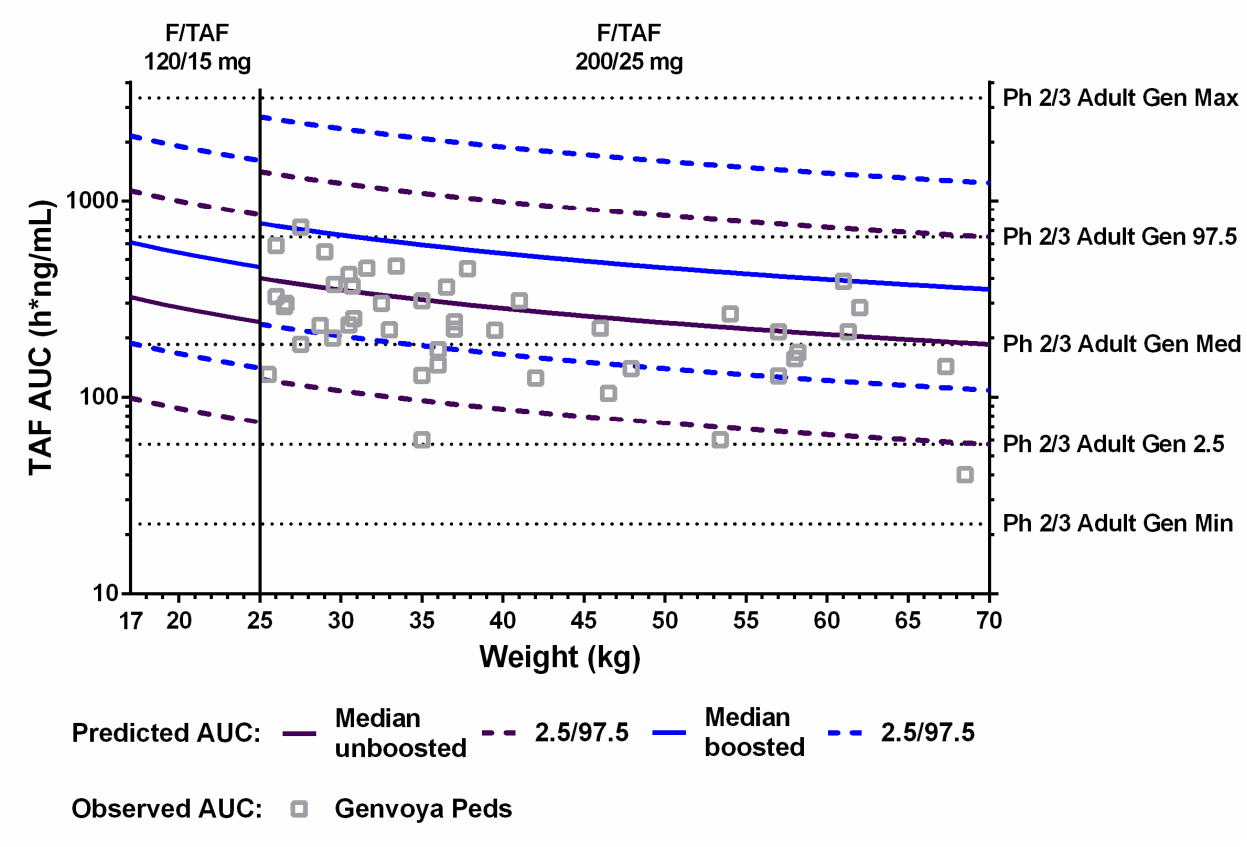
a These doses are regardless of 3rd agent.
b This group will enroll only boosted PIs and this is the dose that will be used.

The dosing nomogram is structured to simplify dosing and formulations and to avoid subtherapeutic dosing in a population requiring lifelong therapy from a young age, in which the implications of virologic failure may be greater than in adults. The predicted exposures following administration of F/TAF 200/25 mg in children weighing ≥ 25 kg or F/TAF 120/15 mg in children weighing 17 to < 25 kg are generally within the range of those observed in adults and simulations of TAF and TFV (TAF-metabolite) exposures for these doses are shown in Figure 1-1 and Figure 1-2 below.

Rationale for TAF Doses in Children 6 to < 12 Years of Age Weighing ≥ 25 kg and Children 2 to 12 Years of Age Weighing 17 to < 25 kg

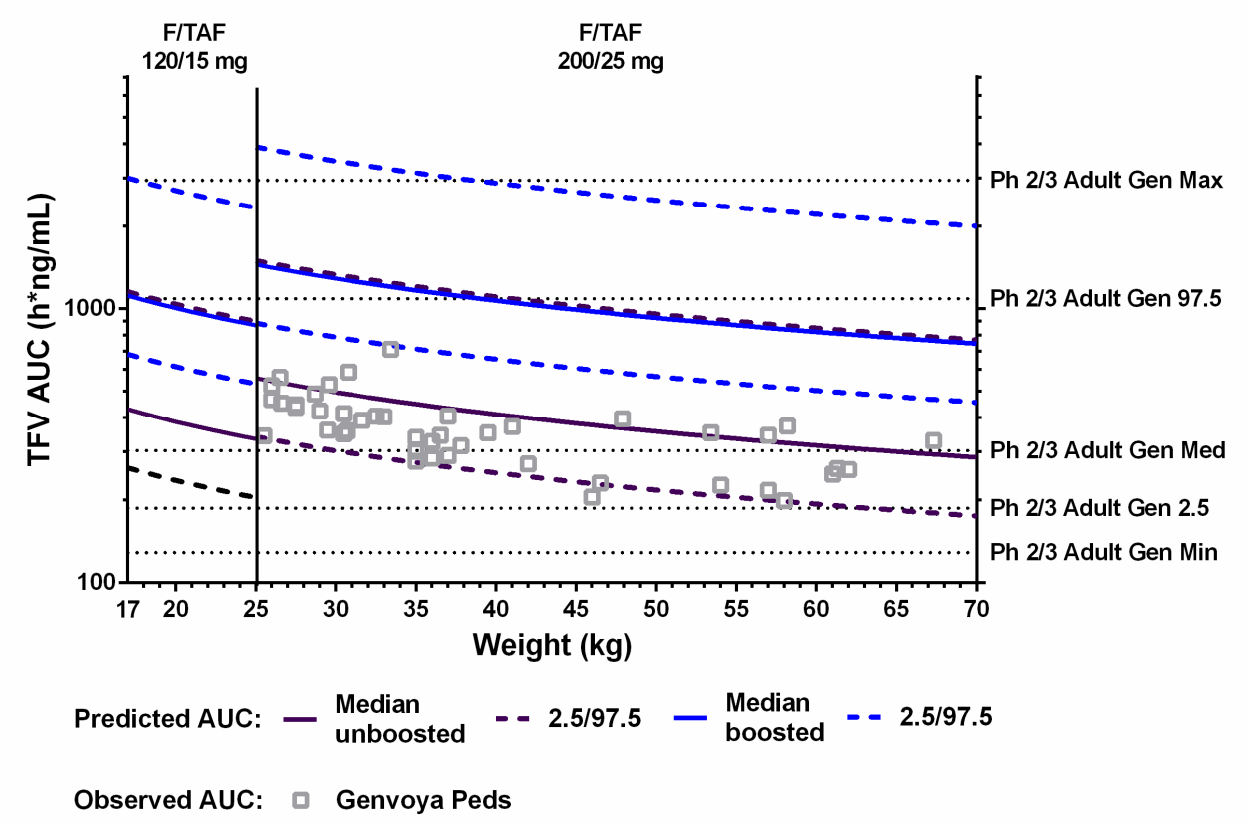
TAF and TFV exposures were predicted by allometric scaling of adult exposures considering correlations between body weight and clearance (CL) capacity. Model-predicted systemic exposures of TAF and TFV in children 6 to < 12 years old and weighing ≥ 25 kg administered F/TAF 200/25 mg or children 2 to < 12 years weighing 17 to < 25 kg with unboosted or boosted 3rd agents are presented in Figure 1-1 and Figure 1-2 respectively. These simulations indicate similar predicted ranges of TAF and TFV exposure in children 6 to < 12 years weighing ≥ 25 kg and children 2 to < 12 years weighing 17 to < 25 kg following administration of F/TAF 200/25 mg or 120/15 mg respectively with unboosted or boosted 3rd agents. Additionally, the range of expected TAF and TFV exposures are generally within the range of those observed in the adult Phase 2/3 population, with TFV exposures that are generally less than median TFV exposures (median AUC: 2360 h*ng/mL) observed in children 6 to < 12 years old with TDF (Study GS-US-104-0352).

Figure 1-1. Predicted TAF AUC in Children Following Administration of F/TAF 200/25 mg or 120/15 mg[a,b,c]



a The adult exposures for TAF were the population PK predicted exposures from GEN Phase 3 studies (Genvoya NDA 207561, m5.3.3.5, Population PK Analysis of TAF and TFV following Administration of E/C/F/TAF STR)
b The observed AUC values for TAF in children ≥ 25 kg are from Study GS-US-292-0106.
c For boosted agents, predicted exposures of TAF upon administration of TAF 25 mg with ATV/r are shown and are expected to encompass exposures of TAF upon coadministration with other boosted 3rd agents (LPV/r or DRV/r) (Table 1-1).

Figure 1-2. Predicted TFV AUC in Children Following Administration of F/TAF 200/25 mg or 120/15 mg[a,b,c]



a The adult exposures for TFV were the population PK predicted exposures from GEN Phase 3 studies (Genvoya NDA 207561, m5.3.3.5, Population PK Analysis of TAF and TFV following Administration of E/C/F/TAF STR)
b The observed AUC values for TFV in children ≥ 25 kg are from Study GS-US-292-0106.
c For boosted agents, predicted exposures of TFV upon administration of TAF 25 mg with ATV/r are shown and are expected to encompass exposures of TFV upon coadministration with other boosted 3rd agents (LPV/r or DRV/r) (Table 1-1).

Rationale for FTC Doses in Children 6 to < 12 Years of Age Weighing ≥ 25 kg and Children 2 to < 12 Years of Age Weighing 17 to < 25 kg

Emtricitabine is approved to be dosed at ≤ 6.1 mg/kg in children as either a capsule or oral solution formulation {EMTRIVA® 2012}. Per the current Emtriva label, the approved dose of 200 mg FTC can be administered in adults with normal renal function and those with mild renal impairment (50-80 mL/min), in whom FTC exposures were shown to be approximately 70% higher than adults with normal renal function {EMTRIVA® 2012}. In addition, a proposal for FTC/TDF low-dose tablets from the WHO Paediatric Antiretroviral Working Group {World Health Organization (WHO) 2011} allows FTC doses up to 8.57 mg/kg (corresponding to a 40% increase over 6.1 mg/kg) for use in children. Given the approved doses for FTC and its dose-proportional pharmacokinetics, the proposed FTC doses for evaluation in children 6 to < 12 years weighing ≥ 25 kg or 2 to < 6 years weighing 17 to < 25 kg are expected to result in exposures in the range of those providing a favorable risk:benefit profile.

The F/TAF FDC tablets for use in patients 6 to < 12 years weighing ≥ 25 kg or 2 to < 6 years weighing 17 to < 25 kg provide a range of FTC doses comparable to the approved doses which do not exceed 8.57 mg/kg.

1.5.3. Dosing in Cohorts 3 (2 to < 6 Years) and 4 (1 Month to < 2 Years)

The protocol will be amended to add dosing and formulation and specific inclusion/exclusion for Cohorts 3 and 4 once dose confirmation is established in Cohort 2.

1.6. Risk/Benefit Assessment for the Study

All patients with HIV-1 infection should receive effective antiretroviral therapy. Potential risks associated with all classes of ARVs include immune reconstitution syndrome, lipodystrophy, and lactic acidosis with steatosis. The risk of class effects is considered to be low. Important identified risks will be appropriately managed by study inclusion/exclusion criteria as well as through close clinical and laboratory monitoring during the study. Interim data will also be reviewed by an independent data monitoring committee. Potential benefits may include provision of a new antiretroviral therapy that is not currently available and which may have fewer side effects than alternative therapies. Other potential benefits include the knowledge that patient participation will contribute to the body of knowledge of HIV therapies.

Potential toxicity is appropriately managed by study inclusion/exclusion criteria, close clinical and laboratory monitoring, as well as specific toxicity management guidance to investigators (refer to Section 7.5.1).

The overall benefit-risk assessment for F/TAF administered orally once-daily with food, in combination with boosted-PI or any other 3rd ARV agent, is favorable at this time.

1.7. Compliance

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

2. OBJECTIVES

The primary objectives of this study are:

- To evaluate the PK of TAF and confirm the TAF dose in HIV-1 infected children and adolescents virologically suppressed on a 2 NRTI-containing regimen.
- To evaluate the safety and tolerability of F/TAF through Week 24.

The secondary objectives of this study are:

- To evaluate the PK of TFV and FTC.
- To evaluate the safety, tolerability, and efficacy of F/TAF through Week 48.

3. STUDY DESIGN

3.1. Primary Endpoints

The primary endpoints are:

- The PK parameter AUC_{tau} for TAF
- Incidence of treatment-emergent SAEs and all treatment-emergent adverse events through Week 24

3.1.1. Secondary Endpoints

The secondary endpoints are:

- PK parameters of C_{max}, C_{last}, Cl/F, and V_z/F for TAF, AUC_{tau}, C_{max}, and C_{tau} for FTC and TFV
- Incidence of treatment-emergent SAEs and all treatment-emergent adverse events through Week 48
- The percentage of subjects with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as defined by the US FDA-defined snapshot algorithm
- The change from baseline in CD4+ cell count (cells/μL) and CD4+ percentage at Weeks 24 and 48
- The palatability and acceptability of the age-appropriate F/TAF formulation

CCI [redacted]

3.2. Study Design

This protocol describes an open-label, multi-cohort switch study to evaluate the PK, safety, and efficacy of F/TAF in HIV-1 infected children (1 month to < 12 years) and adolescents (12 to <18 years) who are virologically suppressed while on a stable 2-NRTI-containing regimen.

A minimum of 100 children and adolescent subjects, 1 month to < 18 years of age of either sex, will be enrolled to receive F/TAF. The study will proceed in sequential cohorts as follows:

3.2.1. Cohort 1 (Adolescents 12 to < 18 years, ≥ 35 kg)

All subjects in Cohort 1 (n = 25) will switch their current 2-NRTI-containing regimen to open-label F/TAF while continuing on their 3rd ARV agent through 48 weeks.

Subjects will be enrolled to evaluate the steady state PK and confirm the dose of TAF.

An intensive PK (IPK) evaluation will be conducted at the Week 2 visit to confirm the dose of TAF and to characterize TFV and FTC exposures as appropriate. Samples will be collected over 24 hours (pre and post dose) and will be analyzed once they are available from all subjects. Replacement subjects may be enrolled if subjects do not complete all IPK procedures or if IPK data is incomplete. Replacement subjects will not be enrolled in Cohort 1 for subjects who discontinue the study due to treatment-related toxicity.

Following completion of the Week 2 IPK visit, all subjects will continue to receive F/TAF plus their 3rd ARV agent and return for study visits through Week 48.

3.2.2. Cohorts 2, 3, and 4

Subjects in Cohorts 2, 3, and 4 must be on a boosted protease inhibitor (PI) (Cohort 2 only) or any other 3rd ARV agent and will switch their current 2-NRTI-containing regimen to open-label F/TAF while continuing their boosted PI or 3rd agent through 48 weeks. A minimum of 10 subjects each in Groups 1 and 2 of Cohort 2, and Cohorts 3 and 4, who are on boosted-ATV as their 3rd ARV agent will be enrolled. Cohorts 2, 3, and 4 will be enrolled by cohort into a two-part study (Parts A and B) as follows:

Part A

A minimum of 67 subjects will be enrolled to evaluate the steady state PK and confirm the dose of TAF with boosted ATV, LPV, DRV or other agents.

Cohort #	Age Range	ATV + F/TAF	LPV or DRV + F/TAF	Other 3rd ARV Agents + F/TAF
2, Group 1[a]	6 to < 12 years	n ≥ 10	n ≥ 6	n/a
2, Group 2[b]	2 to < 12 years	n ≥ 10	n ≥ 7	
3	2 to < 6 years	n ≥ 10	n ≥ 7	
4	1 month to < 2 years	n ≥ 10	n ≥ 7[c]	

a Cohort 2, Group 1 subjects must weigh ≥ 25 kg at screening
b Cohort 2, Group 2 subjects must weigh 17 to < 25 kg at screening
c DRV is not approved for Cohort 4

All subjects in Cohort 2 Part A will undergo an IPK evaluation at either the Week 2 or Week 4 visit or within 7 days after the completion of the Week 2 or Week 4 visit to confirm the dose of TAF and to characterize the exposure of TFV. TAF dose confirmation will be established if the exposure is comparable to that associated with efficacy in adults. Samples will be collected over 8 hours (pre and post dose) and will be analyzed once they are available from all subjects.

Replacement subjects may be enrolled if subjects do not complete all IPK procedures or if the IPK data is incomplete but will not be enrolled for subjects who discontinue the study due to treatment-related toxicity.

Following completion of the IPK, all subjects will continue to receive F/TAF plus their 3rd ARV agent and return for study visits through Week 48.

The IPK collection schedule and fasting requirement for Cohorts 3 and 4 will be specified in a future protocol amendment.

Part B

After confirmation of TAF dose in Part A (IDMC review required) for each cohort (and group for Cohort 2), approximately 10 additional total subjects will receive F/TAF while continuing their 3rd ARV agent through 48 weeks in Part B to evaluate the safety, tolerability and efficacy of the treatment regimen.

3.2.3. Study Procedures and Frequency for All Subjects (All Cohorts and Parts A and B)

At the Screening, Baseline/Day 1, and all subsequent study visits laboratory analyses (hematology, chemistry, and urinalysis), HIV-1 RNA, CD4+ cell count, eGFR using the Schwartz formula, and a complete or symptom directed physical examinations will be performed. Serum (screening) or urine (all other visits) pregnancy tests will be performed on female subjects of childbearing potential.

At screening HBV and HCV serology will be analyzed.

Subjects will return for study visits at Weeks 1, 2, 4, 8, 12, 24, 36, and 48. CCI [redacted]

Tanner stage assessment will be performed at Baseline/Day 1, Weeks 24 and 48, CCI [redacted] or until subjects reach Tanner Stage 5, after which point Tanner assessments will no longer be performed.

Dual energy x-ray absorptiometry (DXA) scans of the lumbar spine and total body will be performed at Baseline/Day 1, Weeks 24 and 48, CCI [redacted] to measure spine bone mineral density (BMD) and total body BMD.

For all subjects, single PK samples will be collected: A single random PK sample will be collected at Weeks 1 and 24, and a single observed dosing PK sample will be collected at any time between 15 min to 4 hours post dose during Weeks 4 and 12 (Note: For subjects in Cohort 2 Part A, a single observed dosing PK sample does not need to be collected at Week 4 if Intensive PK is also collected at the Week 4 visit). A trough sample will be collected at 0 hours (pre-dose, ≤ 30 minutes prior to dosing) during Week 8.

PBMC collection will be performed at sites that have PBMC processing capability. For subjects in Cohorts 1 and 2, PBMC collection will be performed at the Week 8 visit. PBMC collection schedule for Cohorts 3 and 4 will be addressed in a future protocol amendment. For PK profiling in PBMCs, blood samples will be collected at 0 hours (≤ 30 minutes pre-dose). Details of PBMC collection and processing will be documented in the Pharmacokinetic Sample Collection, Processing, Storage, and Shipment Manual (PK manual).

Palatability and acceptability will be assessed in Cohort 1 subjects 30 - 60 minutes after study drug dosing for all subjects undergoing IPK sampling. For Cohort 1 subjects that are currently on study and are beyond the Week 2 visit, an acceptability assessment is required once, preferably at the next clinic visit following the approval of this protocol amendment at the site. Palatability and acceptability will be assessed 30 - 60 minutes after study drug dosing for all subjects undergoing IPK sampling in Part A of Cohorts 2, 3, and 4.

Serum will be collected for bone safety tests (collected fasted), including bone specific alkaline phosphatase (BsAP), serum phosphorous, procollagen type 1-N-terminal propeptide (P1NP), C-type collagen sequence (CTX), parathyroid hormone (PTH), 1,25-OH vitamin D, and 25-OH vitamin D (for Cohort 1: Baseline and Weeks 4, 12, 24, and 48 (±6 days) CCI ; for Cohorts 2,3, and 4: Baseline and Weeks 8, 12, 24, and 48 (±6 days) CCI .

For all cohorts and groups, urine will be collected for urine chemistry, and selected renal safety tests, including retinol binding protein, and beta-2-microglobulin at Baseline/Day 1, Weeks 2, 4, 8, 12, 24, 48, CCI

For Cohorts 1 and 2 (all groups), metabolic assessments will be collected for fasting glucose and lipid panel (total cholesterol, HDL, direct LDL, and triglycerides) at Baseline/Day 1, Weeks 24, 48, CCI

Tanner stage assessment will be performed at Baseline/Day 1, Weeks 24 and 48, CCI , or until subjects reach Tanner Stage 5, after which point Tanner assessments will no longer be performed.

Dual energy x-ray absorptiometry (DXA) scans of the lumbar spine and total body will be performed at Baseline/Day 1, Weeks 24 and 48, CCI to measure spine bone mineral density (BMD) and total body BMD.

CCI subjects who prematurely discontinue prior to Week 48, will be required to return to the clinic 30 days after the completion of the study drug for a 30 Day Follow up visit.

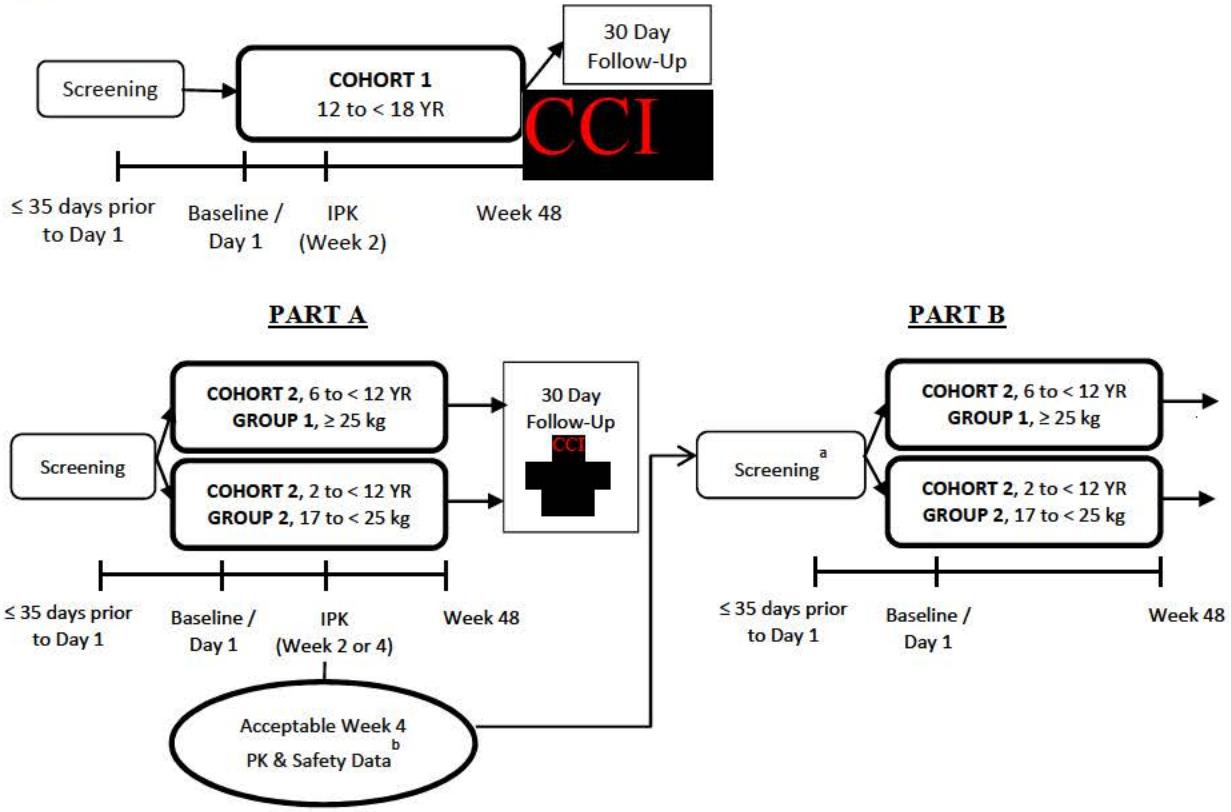
Subjects will receive their assigned treatment for 48 weeks. CCI

[redacted]

CCI

[redacted]

Figure 3-1. Study Schema



a Part B screening will initiate after analysis of intensive PK samples and confirmation of TAF dose in corresponding age cohort in Part A.
b The screening schema for Cohorts 3 and 4 will be specified in a future protocol amendment.

3.3. Study Treatments

In Cohort 1, F/TAF will be administered orally, dosed once-daily in combination with their 3rd ARV agent, at approximately the same time each day, either with or without food, as determined by the subject's 3rd ARV agent.

In Cohorts 2, 3, and 4, F/TAF will be administered orally, dosed once-daily in combination with their 3rd ARV agent, at approximately the same time each day, either with or without food, as determined by the subject's 3rd ARV agent. The F/TAF dose will be based on the subject's weight and 3rd ARV agent.

On the morning of the IPK visit, subjects in Cohort 1 and in Part A of Cohorts 2, 3, and 4 will be administered their dose of study medication in combination with their 3rd ARV agent in the clinic, along with food, prior to IPK sampling. To prepare for the in-clinic dosing, subjects should begin taking study drug and their 3rd ARV agent in the morning starting at least 1 week prior to the IPK visit.

At the single observed dosing PK sampling visit, subjects will be administered their dose of study drug medication in combination with their 3rd ARV agent in the clinic. Prior to the single observed dosing PK sampling visit, subjects should take study drug at approximately the same time each day, regardless of the time of day, for at least 1 week prior to the PK sampling. Subjects will be required to report the time of the last dose during the visit.

Prior to the single random PK sampling visit, subjects should take study drug in combination with their 3rd ARV agent at approximately the same time each day, regardless of the time of day, for at least 1 week prior to the PK sampling. Subjects will be required to report the time of the last dose at the time of the visit.

3.4. Duration of Treatment

Subjects will receive their assigned treatment for 48 weeks. CCI [redacted]

3.5. 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 (i.e., virologic failure as per Section 6.10).
- Subject request to discontinue for any reason.
- Subject noncompliance.

- Pregnancy during the study; refer to Appendix 5.
- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC).

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

A minimum of 100 subjects who meet the eligibility criteria will be enrolled.

4.2. Inclusion Criteria

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

1) HIV-1 infected male and female pediatric patients aged 1 month to < 18 years at Baseline/Day 1 (according to requirements of the enrolling cohort)

2) Subject able to give written assent prior to any screening evaluations if they have the ability to read and write

3) Parent or guardian able to give written informed consent prior to any screening evaluations and willing to comply with study requirements

4) A negative serum β-HCG pregnancy test is required for female subjects of childbearing potential only (as defined in Appendix 5)

5) Body weight at screening as follows:

	Age Range	Weight
Cohort 1	12 years to < 18 years	≥ 35 kg
Cohort 2: Group 1	6 years to < 12 years	≥ 25 kg
Cohort 2: Group 2 (able to swallow a tablet)	2 years to < 12 years	17 kg to < 25 kg
Cohort 3 (unable to swallow a tablet)	2 years to < 6 years	TBD[a]
Cohort 4	1 month to < 2 years	TBD[b]

a Body weight cutoff at screening to be determined based upon analysis of short-term safety and PK data from Cohort 2 Part A before initiating Cohort 3 Part A
b Body weight cutoff at screening to be determined based upon analysis of short-term safety and PK data from Cohort 2 Part A & Cohort 3 Part A

6) Currently on a stable 2-NRTI-containing regimen that includes a 3rd ARV agent for ≥ 6 consecutive months prior to screening.

7) Plasma HIV-1 RNA levels < 50 copies/mL for ≥ 6 consecutive months preceding the screening visit (measured at least twice using the same assay) and not experienced two consecutive HIV-1 RNA above detectable levels after achieving a confirmed (two consecutive) HIV-1 RNA below detectable levels on the current regimen in the past year.

   a) To determine virologic suppression in the preceding 6 months prior to screening, the lower limit of quantification (LLOQ) by the local HIV-1 RNA assay may be used, only if its LLOQ is greater than 50 copies/mL (e.g. LLOQ of 75 copies/mL).

8) Estimated glomerular filtration rate (eGFR) ≥ 90 mL/min/1.73m^2 by (Schwartz) formula

9) All male subjects and those female subjects of childbearing potential or those who reach childbearing potential during study participation (as defined in Appendix 5) 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 Appendix 5 for definition of females of childbearing potential.

10) 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.

11) Adequate hematologic function defined as:

    a) Absolute neutrophil count ≥ 500 cells/mm^3 (Subjects with neutrophil count of < 500/mm^3 documented at least twice within 6 months of screening, and in who, according to the investigator, there is no evidence of immunosuppression associated with low neutrophil count, can enroll in the study contingent upon approval from the Gilead study Medical Monitor.)

    b) Hemoglobin > 8.5 g/dL

    c) Platelets ≥ 50,000/mm^3

12) Hepatic transaminases (AST and ALT) ≤ 5 × upper limit of normal (ULN)

13) For subjects on all 3rd ARV agents except ATV, total bilirubin ≤ 1.5 mg/dL or normal direct bilirubin

14) For subjects on ATV, total bilirubin ≤ 3.0 mg/dL or normal direct bilirubin

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

16) Must be willing and able to comply with all study requirements

17) No opportunistic infection within 30 days of study entry (at Baseline/Day 1)

18) Subject is able to swallow a tablet

4.3. Exclusion Criteria

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

1) An acquired immunodeficiency syndrome (AIDS)-defining condition with onset within 30 days prior to screening

2) Life expectancy of < 2 years.

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

4) Evidence of active pulmonary or extra-pulmonary tuberculosis disease within 3 months of the screening visit

5) Anticipated requirement for rifamycin treatment while participating in the study.
Note: prophylactic isoniazid therapy for latent tuberculosis is allowed.

6) Active HCV infection defined as positive for HCV antibody and having detectable HCV RNA.

    a) Note: subjects with positive HCV antibody and without detectable HCV RNA are permitted to enroll.

7) Positive hepatitis B surface antigen or other evidence of active HBV infection.

    a) Note: Subjects with positive HBV surface antibody and no evidence of active HBV infection are permitted to enroll.

8) Subjects with a historical genotype that have documented or suspected resistance to TFV or FTC, including, but not limited to, the presence of reverse transcriptase mutations K65R, K70E, M184V/I, or 3 or more thymidine analog-associated mutations (TAMs) that include M41L or L210W (TAMs are M41L, D67N, K70R, L210W, T215Y/F, K219Q/E/N/R).

9) 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 or active tuberculosis), 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 Baseline/Day 1).

10) Subjects experiencing decompensated cirrhosis (e.g., ascites, encephalopathy).

11) A history 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 screening and are not anticipated to require systemic therapy during the study.

12) Pregnant or lactating subjects

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

14) Have history of significant drug sensitivity or drug allergy.

15) Known hypersensitivity to the investigational medicinal product (IMP), the metabolites, or formulation excipient.

16) Have previously participated in an investigational trial involving administration of any investigational agent, other than TDF, within 30 days prior to the study dosing.

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

18) Subjects receiving ongoing therapy with any of the following medications in the table below, including drugs not to be used with FTC, TAF or their 3rd ARV agent (refer to the individual agents Prescribing Information).

Table 4-1. Prohibited Medication while on Study

Medication Class	Prohibited Medications
Anticonvulsants	carbamazepine, oxcarbazepine, phenobarbital, phenytoin
Antimycobacterials	rifapentine, rifabutin, rifampin
Antivirals	cidofovir, ganciclovir, valganciclovir
Herbal/Natural Supplements	St. John's Wort, Echinacea, Milk thistle (i.e., silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang)
Other	probenecid

* Administration of any of the above prohibited medications must be discontinued at least 30 days prior to the Baseline/Day 1 visit and for the duration of the study.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Enrollment

This is an open-label study.

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

Subjects will be assigned a screening number at the time of consent.

The enrollment and Baseline/Day 1 visit cannot occur until subject eligibility has been confirmed. Once eligibility is confirmed, the study site will use the IWRS to assign a unique subject enrollment number. Once a subject number has been assigned to a subject it will not be reassigned to any other subject.

The subject number assignment and enrollment may be performed up to 7 days prior to the Baseline/Day1 visit provided that all screening procedures have been completed and subject eligibility has been confirmed by the Sponsor.

All subjects will switch their current 2-NRTI-containing regimen to F/TAF while continuing their protocol-specified 3rd ARV agent.

IWRS will assign study drug bottle numbers for dispensing study drug at study visits. Initiation of treatment with the study drug must take place within 24 hours after the Baseline/Day 1 visit.

5.2. Description and Handling

5.2.1. Formulations

5.2.1.1. Emtricitabine/Tenofovir Alafenamide (F/TAF)

5.2.1.1.1. Emtricitabine 200 mg/Tenofovir Alafenamide 25 mg tablets

Emtricitabine 200 mg/Tenofovir Alafenamide 25 mg tablets are rectangular-shaped, film-coated blue tablets that are debossed with "GSI" on one side of the tablet and "225" on the other side of the tablet. The F/TAF tablet cores contain 200 mg of emtricitabine and 25 mg of tenofovir alafenamide. In addition to the active ingredients, the F/TAF tablets contain croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The tablet cores are film coated with FD&C Blue #2/indigo carmine aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

5.2.1.1.2. Emtricitabine 200 mg/Tenofovir Alafenamide 10 mg tablets

Emtricitabine 200 mg/Tenofovir Alafenamide 10 mg tablets are rectangular-shaped, film-coated gray tablets that are debossed with "GSI" on one side of the tablet and "210" on the other side of the tablet. The F/TAF tablet cores contain 200 mg of emtricitabine and 10 mg of tenofovir alafenamide. In addition to the active ingredients, the F/TAF tablets contain croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The tablet cores are film coated with iron oxide black, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

5.2.1.1.3. Emtricitabine 120 mg/Tenofovir Alafenamide 15 mg tablets

Emtricitabine 120 mg/Tenofovir Alafenamide 15 mg tablets are round, plain faced, film-coated white tablets. Alternatively F/TAF 120/15 mg tablets are round, debossed with “GSI” on one side of the tablet and “15” on the other side, film-coated white tablets. The F/TAF tablet cores contain 120 mg of emtricitabine and 15 mg of tenofovir alafenamide. In addition to the active ingredients, the F/TAF tablets contain croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The tablet cores are film coated with polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

5.2.2. Packaging and Labeling

Emtricitabine/Tenofovir Alafenamide (F/TAF) tablets are packaged in a white high density polyethylene (HDPE) bottle. Each bottle contains 30 tablets, silica gel desiccant, and polyester packing material. Each bottle is capped with a white, continuous thread, child-resistant, polypropylene screw cap fitted with an induction-sealed, aluminum-faced liner.

Study drug(s) to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the United States Food and Drug Administration (FDA), EU Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products), and/or other local regulations. All labels for study drug bottles to be distributed to centers in the US, EU and the rest of the countries will meet all applicable requirements of the US Food and Drug Administration (FDA) and Annex 13 of Good Manufacturing Practices: Manufacture of investigational medicinal products (February 2010) and/or other local regulations as applicable.

5.2.3. Storage and Handling

Emtricitabine/Tenofovir Alafenamide (F/TAF) should be stored at a controlled room temperature of 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F).

Storage conditions are specified on the label. Until dispensed to the subjects, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure the stability and proper identification, study drug(s) should not be stored in a container other than the container in which they were supplied. Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure through inhalation when handling.

5.3. Dosage and Administration

All subjects in Cohort 1 will switch their current 2-NRTI-containing regimen to F/TAF while continuing their 3rd ARV agent. All subjects in Cohorts 2, 3, and 4 will switch their current 2-NRTI-containing regimen to F/TAF and must be on a boosted-PI or other agent as their 3rd ARV agent as applicable per cohort.

5.3.1. Cohort 1 (12 years to < 18 years, ≥ 35 kg)

F/TAF fixed-dose combination tablets will be provided by Gilead Sciences and will be administered orally, once daily as noted below in Table 5-1. The 3rd ARV agent will be prescribed by the Investigator and the subject will be responsible for obtaining the 3rd ARV agent prior to Baseline/Day 1 visit.

During the study, investigators wishing to change a subject's 3rd ARV agent for reasons other than virologic failure must discuss this change with the Gilead Medical Monitor. Refer to Section 6.10 for more information.

At the IPK and at the single observed dosing PK sampling visits at Weeks 4 and 12, subjects will be administered their dose of study medication and their 3rd ARV agent in the clinic with food prior to the PK sampling.

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Table 5-1. Cohort 1 Dosing Recommendation for F/TAF in combination with 3rd ARV Agents

Cohort	Age and body weight	F/TAF dose (mg) with 3rd agent
1	12 to < 18 years, ≥ 35 kg	200/25 for unboosted 3rd agent 200/10 for boosted 3rd agent

5.3.2. Cohorts 2, 3, and 4

F/TAF fixed-dose combination tablets will be provided by Gilead Sciences and will be administered orally, once daily as noted above in Table 5-1. The subject's 3rd ARV agent will be prescribed by the Investigator and the subject will be responsible for obtaining the 3rd ARV agent prior to Baseline/Day 1 visit.

For subjects in Part A of Cohorts 2, 3, and 4, at the IPK visit and at the single observed dosing PK sampling visits, subjects will be administered their dose of study medication and their 3rd ARV agent in the clinic with food prior to the PK sampling.

Table 5-2. Cohorts 2, 3, and 4 Dosing Recommendations for F/TAF

Cohort	Age and body weight	F/TAF dose (mg)
2, Group 1	6 to < 12 years, ≥ 25 kg	200/25
2, Group 2 (able to swallow a tablet)	2 to < 12 years, ≥ 17 to < 25 kg	120/15
3 (unable to swallow a tablet)	2 to < 6 years, TBD	TBD[a]
4	1 month to < 2 years, TBD	TBD[a]

a Dosage, using weight appropriate F/TAF dispersible tablets prepared as an oral suspension, will be specified by protocol amendment after clinical safety, efficacy, and PK data from Cohorts 1 and 2 are available to guide dose selection of F/TAF to be administered in Cohorts 3 and 4. Subjects under 6 years of age who cannot swallow tablets will be allowed to choose this formulation for treatment as well.

5.4. Prior and Concomitant Medications

The use of medications for the treatment of HIV, other than the study treatment (i.e., F/TAF) and baseline 3rd ARV agent, is prohibited. Medications listed in Table 5-3 and use of herbal/natural supplements are excluded or should be used with caution while subjects are participating in the study due to potential drug-drug interactions with the study drugs.

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

Table 5-3. List of Prohibited Medications and Medications That Are To Be Used With Caution

Medication Class	Prohibited Medications	Medications To Be Used With Caution
Antiarrhythmics		amiodarone, quinidine: May increase concentration of TAF and/or TFV
Anticonvulsants	carbazepine, oxcarbazepine, phenobarbital, pheynytoin	
Antimycobacterials	rifapentine, rifabutin, rifampin	clarithromycin: may increase concentration of TAF and/or TFV
Antifungals		itraconazole, ketoconazole, voriconazole: may increase concentration of TAF and/or TFV
Antivirals	cidofovir, ganciclovir, valganciclovir	acyclovir, valacyclovir
Calcium channel blockers		diltiazem, felodipine, verapamil: may increase concentration of TAF and/or TFV
Digoxin		Concomitant use may result in an increased or decreased digoxin concentration; use with caution and with appropriate monitoring of serum digoxin concentrations.
Herbal/Natural Supplements	St. John's wort, Echinaccea, Milk thistle (i.e. silymarin), Chinese herb sho-saiko-to (or Xiao-Shai-Hu-Tang	
Others	Probenecid	

Medications listed in Table 5-4 are prohibited and should be discussed with the GSI Medical Monitor while subjects are participating in the study due to potential adverse skeletal effects.

Table 5-4. List of Prohibited Medications with Adverse Skeletal Effects

Medication Class	Prohibited Medications
Cyclophosphamides / Cytophosphanes	cytoxan, endoxan, neosar, procytox, revimmune
Ciclosporins	cyclosporine A, B, C, D, E, F, and G
Glucocorticoids	Chronic, systemic glucocorticoids
Medroxyprogesterones	Depo-Provera

Additionally, Investigators should refer to the product/package inserts of the other ARV medications for age-related recommendations or contraindications related to their use.

5.5. Accountability

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.

F/TAF accountability records will be provided to each study site to:

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

5.6. Investigational Medicinal Product Return or Disposal

Refer to Section 9.1.7 for detailed instructions.

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 also described in the text that follows.

Any deviation from protocol procedures should be noted in the subject's clinical chart and electronic Case Report Forms (eCRFs). In addition, the Sponsor or Contract Research Organization (CRO) should be promptly notified of any important protocol deviations.

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 and treatment assignment for each Cohort.

6.2. Pretreatment Assessments

6.2.1. Screening Visit

Subjects will be screened within 35 days before Baseline/Day 1 to determine eligibility for participation in the study. The following activities will be performed and documented during screening:

- Obtain written informed assent/consent

  Each subject must sign an assent if they have the ability to read and write (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.

- Obtain medical and medication history, including history of:

  — Review of Concomitant Medications

    ■ Any ongoing medications within 30 days of the Screening visit

  — HIV-1 disease-related events

  — Historical genotypes should be collected, if available.

- Complete physical examination (urogenital/anorectal examination will be performed at the discretion of the investigator)

- Vital signs (blood pressure, pulse, respiration rate, and temperature)

- Weight and height/length
- 12-lead ECG performed supine
- Urine collection for the following laboratory procedures:
  - Urinalysis
- Blood sample collection for the following laboratory analyses:
  - Serum pregnancy test (for females of childbearing potential in **Cohorts 1 & 2 only**). If the test is positive, the subject will not be enrolled.
  - Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN)
  - Hematology profile: complete blood count (CBC) with differential and platelet count
  - Estimated Glomerular Filtration Rate (eGFR) using Schwartz Formula:
    - (mL/min/1.73 m^2) = k × L/S_{Cr} (k is a proportionality constant, L is height in centimeters (cm) and S_{Cr} is serum creatinine (mg/dL)).
      - The value of k is 0.55 for children (≥ 2 to < 12) and adolescent girls (≥ 12 years old) and 0.7 for adolescent boys (≥ 12 years old).
  - Plasma HIV-1 RNA
  - CD4+ cell count and percentage
  - Hepatitis B virus (HBV) surface antigen serology (HBsAg)
  - Hepatitis C virus antibody (HCVAb) serology
    - Note: If the antibody test result is positive, HCV RNA test will be performed to confirm HCV viremia.
- Record any serious adverse events and all adverse events related to protocol mandated procedures occurring after signing of the consent form.

6.2.2. Baseline/Day 1 Assessments

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 1visit.

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.

From the time of obtaining informed consent and subject assent through the first administration of investigational medicinal product, 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. Refer to Section 7, Adverse Events and Toxicity Management, for additional details.

The following items and evaluations are to be completed at the Baseline/Day 1 Visit. The subject must complete all Baseline/Day 1 procedures before being dispensed the study drug. Initiation of treatment with the study drug must take place within 24 hours after the Baseline/Day 1 visit.

- Review of AEs and changes in concomitant medications
- Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the Investigator)
- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature)
- Weight and height/length
- Tanner Stage assessment
- DXA Scan of the lumbar spine and of the total body for BMD:
  - The DXA scan will be performed on subjects once eligibility is confirmed and prior to study drug administration at the Baseline/Day 1 Visit. The scan may be performed on the morning of the Baseline/Day 1 Visit as long as it occurs before dosing.
- Urine collection for the following laboratory procedures:
  - Urinalysis
  - Urine Chemistry

— Urine renal safety test (collected fasted for Cohorts 1 and 2) including retinol binding protein and beta-2-microglobulin. If the subject has not fasted prior to the visit, the visit may continue; however, the subject must return within 72 hours in a fasted state to provide a urine sample for renal safety test. The fasting requirement for Cohorts 3 and 4 will be specified in a future protocol amendment.

— Urine pregnancy test (females of childbearing potential in **Cohorts 1 & 2 only**). If the urine pregnancy test is positive at Baseline/Day 1, study drug will not be dispensed. The positive result will be confirmed with a serum pregnancy test. If the serum pregnancy test is positive the subject will not be able to participate.

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- Blood sample collection for the following laboratory analyses:

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

— Metabolic assessments: Fasting (no food or drinks, except water, at least 5 hours prior to blood collection) glucose and lipid panel (total cholesterol, HDL, direct LDL, and triglycerides) for Cohorts 1 and 2 (all groups). If the subject has not fasted prior to the visit, the visit may continue; however, the subject must return within 72 hours in a fasted state to draw blood for the metabolic assessments. The fasting requirement for Cohorts 3 and 4 will be specified in a future protocol amendment.

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

— Plasma HIV-1 RNA

— CD4+ cell count and percentage

CCI [redacted]

— Whole blood sample storage for virology testing

— Serum will be collected for bone safety tests (collected fasted), including bone specific alkaline phosphatase (BsAP), serum phosphorous, P1NP, CTX, PTH, 1,25-OH vitamin D, and 25-OH vitamin D. If the subject has not fasted prior to the visit, the visit may continue; however, the subject must return within 72 hours in a fasted state to draw blood for bone safety tests.

— eGFR using Schwartz Formula

- Assign subject number:

  The subject's enrollment number can be assigned via IWRS up to 7 days prior to the Baseline/Day 1 visit provided that all screening procedures have been completed and subject eligibility has been confirmed.

- Study drug dispensation:

  Study drug will be dispensed in an open-label fashion. Subjects and/or parent/guardian will be dispensed F/TAF based on cohort, their weight and their 3rd agent. Subjects should initiate dosing of study drug within 24 hours after the Baseline/Day 1 visit. Investigators will provide prescriptions to the subjects and/or parent/guardian for their 3rd ARV agent. The subjects and/or parent/guardian are responsible for obtaining their 3rd ARV agent prior to the Baseline/Day 1 visit.

  Subjects and/or parent/guardian should be instructed to take study drug along with the subject's 3rd ARV agent once daily with or without food as determined by the 3rd ARV agent and at approximately the same time each day. The subject and/or parent/guardian should be counseled regarding the importance of adherence and taking all their ARV study medication at approximately the same time each day. Sites should consider individual subject study drug dosing schedules while scheduling study visits requiring collection of PK samples.

- Study drug accountability:

  Subjects and/or parent/guardian should be reminded to bring their drug bottles of the F/TAF and their 3rd ARV agent with them for drug accountability at Week 1.

6.3. Treatment Assessments through 48 Weeks (Weeks 1 (Day 7) − 48)

The following evaluations are to be completed at the end of **Weeks 1 (Day 7), 2, 4, 8, 12, 24, 36, and 48** unless otherwise specified.

All study visits are to be scheduled relative to when the Baseline/Day 1 visit was completed. Thereafter all study visits through Week 8 are to be completed within ± 2 days of the protocol specified visit date. Visits between Week 12 through Week 48 are to be completed within ± 4 days of the protocol specified visit date, unless otherwise specified.

Regularly scheduled evaluations will be made on all subjects whether or not they continue to receive study drug.

- Review of AEs and changes in concomitant medications

- Complete physical examination **(Weeks 24 and 48)** (urogenital/anorectal exams will be performed at the discretion of the Investigator) or symptom-directed physical examination as needed **(Week(s) 1 (on Day 7), 2, 4, 8, 12, and 36)**

- Vital signs (blood pressure, pulse, respiration rate, and temperature)
- Weight and height/length
- Tanner Stage assessment **(Weeks 24 and 48 - except for subjects documented to have achieved Tanner Stage 5)**
- DXA Scan of the lumbar spine and the total body for BMD **at Weeks 24 and 48 (± 10 days)**
- Urine collection for the following laboratory procedures:
  - Urinalysis
  - Urine chemistry **(Weeks 2, 4, 8, 12, 24, and 48)**
  - Selected renal safety test (collected fasted for Cohorts 1 and 2) including retinol binding protein and beta-2-microglobulin. If the subject has not fasted prior to the visit, the visit may continue; however, the subject must return within 72 hours in a fasted state to provide a urine sample for renal safety test **(Weeks 2, 4, 8, 12, 24, and 48)**.
  - Urine pregnancy test (females of child bearing potential in **Cohorts 1 & 2 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 be discontinued.

CCI [redacted]

- Blood collection for the following laboratory procedures:
  - Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN).
  - Metabolic assessments: Fasting (no food or drinks, except water, at least 5 hours prior to blood collection) glucose and lipid panel (total cholesterol, HDL, direct LDL, and triglycerides) for Cohorts 1 and 2. If the subject has not fasted prior to the visit, the visit may continue; however, the subject must return within 72 hours in a fasted state to draw blood for the metabolic assessments. Fasting requirement for Cohorts 3 and 4 will be specified in a future protocol amendment **(Weeks 24 and 48)**.
  - Hematology profile: complete blood count (CBC) with differential and platelet count
  - Plasma HIV-1 RNA

— CD4+ cell count and percentage

CCI [redacted]

— Serum for bone safety tests (collected fasted), including bone specific alkaline phosphatase (BsAP), serum phosphorous, P1NP, CTX, PTH, 1,25-OH vitamin D, and 25-OH vitamin D. If the subject has not fasted prior to the visit, the visit may continue; however, the subject must return within 72 hours in a fasted state to draw blood for bone safety tests **(for Cohort 1: Weeks 4, 12, 24, and 48 (±6 days); for Cohorts 2,3, and 4: Weeks 8, 12, 24, and 48 (±6 days))**

— eGFR according to Schwartz formula

- Diary card dispensation:

  — Cohort 1: Dispense subject diary cards for subject to record administration of study drugs and their 3rd ARV agent for at least 3 days prior to the IPK visit **(Week 2)**.

  — Cohorts 2, 3, and 4, Part A: Dispense subject diary cards for subject and/or parent/guardian to record administration of study drugs and their 3rd ARV agent for at least 3 days prior to the IPK visit **(Week 2 or 4)**.

- Study drug dispensation:

  — In-clinic dosing will occur at Weeks 2, 4, 8, and 12

  — Document study drug dispensation for all study drugs dispensed (**Weeks 4, 8, 12, 24, 36** [redacted]

  — The subject should be counseled regarding the importance of adherence and taking their study medication and their 3rd ARV agent, once daily, at approximately the same time each day as directed by the Investigator. Sites should consider individual subject study drug dosing schedules while scheduling study visits requiring collection of PK samples.

- Study drug accountability:

  — Subjects and/or parent/guardian should be reminded to bring their drug bottles of the F/TAF and their 3rd ARV agent with them to each visit for drug accountability **(Weeks 1, 2, 4, 8, 12, 24, 36, and 48)**.

- Subjects who meet the criteria for rebound should be managed according to Management Virologic Failure Section 6.10.

- PK Blood Collection:

  — Intensive PK:

    - IPK samples will be collected for IPK evaluation for fasted subjects in Cohort 1 during the Week 2 visit and for fasted subjects in Cohort 2 Part A during either the Week 2 or the Week 4 visit or within 7 days after the completion of Week 2 or the Week 4 visit, as detailed in the PK manual. The protocol will be amended prior to Cohorts 3 and 4 screening. The IPK collection schedule and fasting requirement for Cohorts 3 and 4 will be specified in a future protocol amendment.

    - Details of the IPK blood sampling procedures, and sample management will be documented in the Pharmacokinetic Sample Collection, Processing, Storage, and Shipment Manual (PK manual). Subject diary cards will be provided to subjects and/or parent/guardian to record administration of study drugs and their 3rd ARV agent for at least 3 days prior to the PK visit.

    - Subjects and/or parent/guardian should be instructed prior to the IPK visit that on the day of IPK evaluations they should be fasted and that their dose of F/TAF and their 3rd ARV agent must **not** be taken prior to the visit. This is not applicable to the visits when the random PK sample is drawn.

    - If the subject has already dosed prior to the IPK evaluation visit or is not in a fasted state, the IPK assessments must not be completed. The subject should be instructed to return in a fasted state anytime within 7 days and to return completed Diary Cards.

    - If dosing non-compliance not related to AEs is identified on or prior to the IPK evaluation visit, the IPK assessments must not be completed. The subject should be counseled regarding proper dosing and be scheduled to return for the IPK evaluation visit no sooner than 3 days following compliant dosing and within 7 days and to return completed Diary Cards.

    - In both scenarios described above the subject and/or parent/guardian should be reminded again to be fasted and to **not** take the F/TAF or their 3rd ARV agent prior to arriving at the clinic on the day of the re-scheduled Intensive PK visit.

    - Subject dosing diaries will be collected and reviewed on the day of the IPK study visit.

— Single PK:

  - Cohort 1: A single random PK sample will be collected at Weeks 1 and 24, and a single observed PK dosing sample will be collected at any time between 15 min to 4 hours post dose during Weeks 4 and 12 and a trough PK sample at 0 hours (pre-dose, ≤ 30 minutes prior to dosing) during the Week 8 visit.

  - Cohorts 2, 3, and 4: A single random PK sample will be collected at Weeks 1 and 24, and a single observed PK dosing sample will be collected at any time between 15 min to 4 hours post dose during Weeks 4 and 12 (Note: Single observed dosing PK sample does not need to be collected at Week 4 if Intensive PK is also collected at the Week 4 visit). Trough PK sampling will be performed at the Week 8 visit at 0 hours (pre-dose, ≤ 30 minutes prior to dosing).

- Palatability and Acceptability Assessment:

  — Cohort 1: At the Week 2 visit palatability will be assessed 30 - 60 minutes after study drug dosing for all subjects undergoing IPK sampling. Acceptability will be assessed 30 - 60 minutes after study drug dosing for active subjects at the next study visit immediately following approval of this protocol at the site.

  — Cohorts 2 Part A: Palatability and acceptability will be assessed at the Week 2 or Week 4 visit, or within 7 days after the completion of the Week 2 or Week 4 visit, 30 - 60 minutes after study drug dosing for all subjects undergoing IPK sampling.

  — Cohorts 3 and 4 Part A: Palatability and acceptability will be assessed for subjects undergoing IPK sampling. Assessment schedule will be specified in a future protocol amendment.

- PBMC Collection (at centers that have PBMC processing capability):

  — Cohorts 1 and 2: PBMC collection will be performed during the Week 8 visit only at study sites that can perform PBMC processing.

  — Cohorts 3 and 4: PBMC collection schedule will be specified in a future protocol amendment.

  — For PK profiling in PBMCs, blood samples will be collected at 0 hours (≤ 30 minutes pre-dose). Details of PBMC collection and processing will be documented in the PK manual.

6.4. Early Study Drug Discontinuation (ESDD)

If a subject discontinues study drug prior to Week 48, the subject 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. CCI [redacted]

At the ESDD 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.

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

- Review of AEs and concomitant medications
- Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the Investigator)
- Vital signs (blood pressure, pulse, respiration rate, and temperature)
- Weight and height/length
- 12-lead ECG performed supine
- Urine collection for the following procedures:
  - Urinalysis and urine chemistry
  - Urine pregnancy test (for females of childbearing potential in Cohorts 1 and 2 only). The positive result will be confirmed with a serum pregnancy test.
  - CCI [redacted]
  - Selected renal safety test, including retinol binding protein and beta-2-microglobulin (renal safety tests required if last test was acquired > 12 weeks from the date of the ESDD Visit (collected fasted for Cohorts 1 and 2). If the subject has not fasted prior to the visit, the visit may continue; however, the subject must return within 72 hours in a fasted state to provide a urine sample for renal safety test).

- Blood sample collection for the following laboratory analyses:
  - Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CPK, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × ULN)
  - eGFR according to Schwartz formula
  - Hematology profile: complete blood count (CBC) with differential and platelet count
  - CD4+ cell count and percentage
  - Plasma HIV-1 RNA
  - CCI [redacted]
  - Serum storage sample for possible additional testing
  - Serum will be collected for bone safety tests (collected fasted), including bone specific alkaline phosphatase (BsAP), serum phosphorous, P1NP, CTX, PTH, 1,25-OH vitamin D, and 25-OH vitamin D. If the subject has not fasted prior to the visit, the visit may continue, however the subject must return within 72 hours in a fasted state to draw blood for bone safety tests.
- DXA scan (lumbar spine and total body) required if last scan was acquired > 12 weeks from the date of the ESDD Visit. DXA scan can occur up to 10 days after the ESDD Visit.
- Drug accountability

6.5. 30-Day Follow-Up Visit

Subjects who discontinue study drug prior to Week 48 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 Early Study Drug Discontinuation Visit will not be required to complete the 30-Day Follow-Up visit.

CCI [redacted]

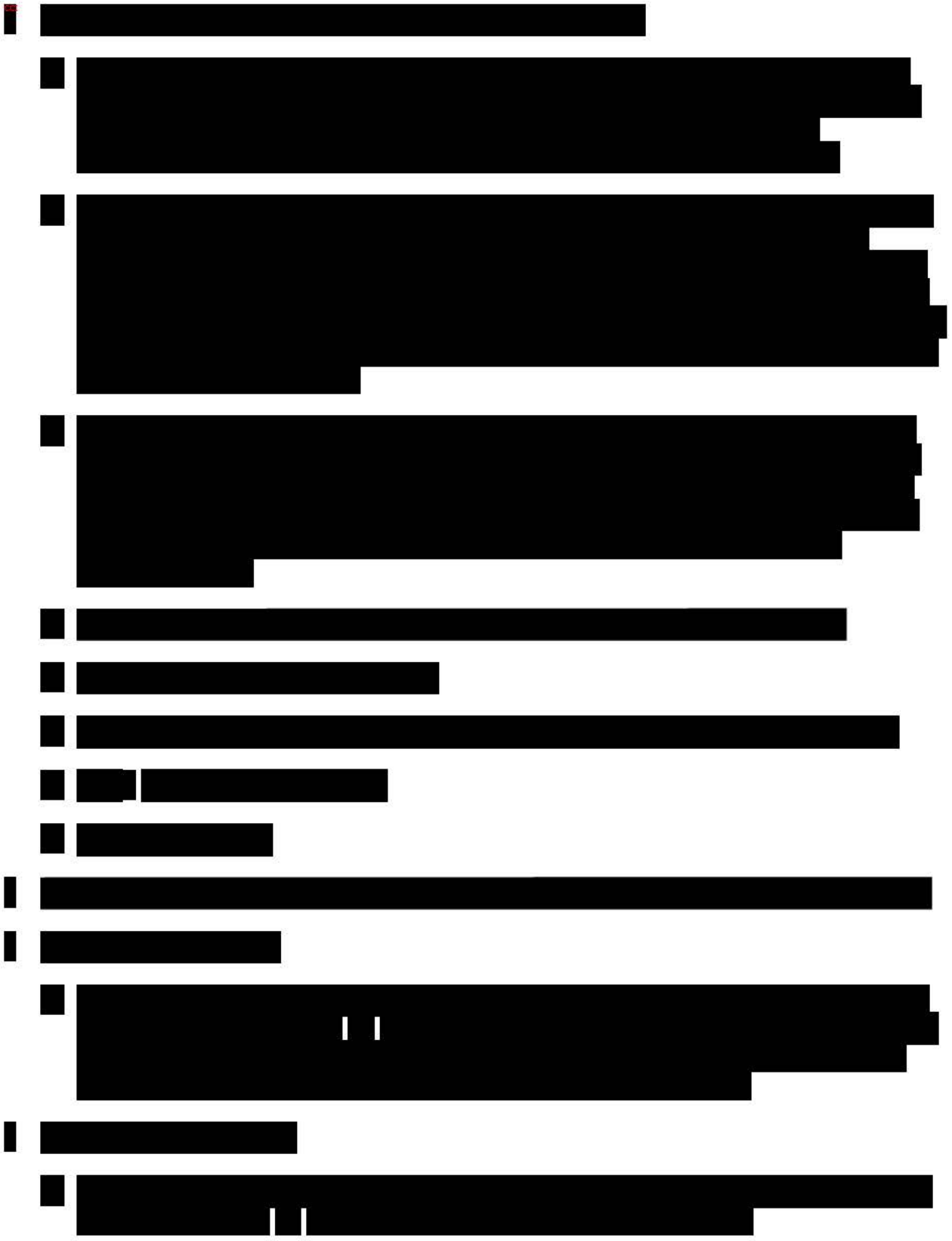
For the purpose of scheduling a 30-Day Follow-Up visit, a ± 6 days window may be used.

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

- Review of AEs and concomitant medications
- Symptom-directed physical examination
- Vital signs (blood pressure, pulse, respiration rate, and temperature)
- Weight and height/length
- Urine collection for the following procedures:
  - Urinalysis
  - Urine pregnancy test (for females of childbearing potential only for Cohorts 1 and 2). A positive result will be confirmed with a serum pregnancy test.
  - CCI [redacted]
- DXA scan (lumbar spine and total body) required if last scan was acquired > 12 weeks from the date of the 30 day follow-up Visit. DXA scan can occur up to 10 days after the 30 day follow-up Visit.
- Blood sample collection for the following laboratory analyses:
  - Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, magnesium, potassium, and sodium, CPK, and uric acid
  - eGFR according to Schwartz formula
  - Hematology profile: complete blood count (CBC) with differential and platelet count
  - CD4+ cell count and percentage
  - Plasma HIV-1 RNA
  - Serum storage sample for possible additional testing

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.

[redacted]



6.7. Bone Evaluations

For all subjects DXA scans will be performed prior to study drug administration at the Baseline/Day 1, at Weeks 24 and 48 (±10 days), CCI [redacted], and the Early Study Drug Discontinuation Visit (if applicable) up to 10 days after the ESDD visit date. Scans will cover the lumbar spine and total body to measure changes in bone mineral density (BMD). DXA scan results will be provided to study sites.

A complete description of the procedures performed for the DXA scans will be provided in a DXA manual.

6.8. Bone and Renal Safety Evaluations

For subjects in Cohort 1, the following bone safety tests will be collected (fasted) at Baseline/Day 1 and Weeks 4, 12, 24, and 48 (±6 days), CCI [redacted]: BsAP, P1NP, CTX, PTH, 1,25-OH vitamin D, and 25-OH vitamin.

For subjects in Cohort 2, 3, and 4, the following bone safety tests will be collected (fasted) at Baseline/Day 1 and Weeks 8, 12, 24, and 48 (±6 days), CCI [redacted]: BsAP, P1NP, CTX, PTH, 1,25-OH vitamin D, and 25-OH vitamin.

For all subjects, urine will also be collected for selected renal safety tests, including urine chemistry, retinol binding protein, and beta-2-microglobulin at the Baseline/Day 1 Visit, Weeks 2, 4, 8, 12, 24, and 48, CCI [redacted]

Bone and renal safety test assessments will be collected fasted. If the subject has not fasted prior to the visit, the visit may continue; however, the subject must return within 72 hours in a fasted state to draw blood for bone safety tests and provide a urine sample for renal safety tests.

CCI [redacted]

[redacted]

[redacted]

CCI [redacted]

6.10. Virologic Failure and Management of Virologic Rebound

Subjects who experience virologic rebound (VR), as defined below, will be considered to have virologic failure.

If the viral load is ≥ 50 copies/mL, HIV-1 RNA should be repeated at a scheduled or unscheduled visit (2-4 weeks after the date of the original test with HIV-1 RNA ≥ 50 copies/mL).

Subjects will be considered to have virologic rebound if they have confirmed HIV-1 RNA ≥ 50 copies/mL (two consecutive tests) at scheduled or unscheduled visits.

Upon confirmation of HIV-1 RNA ≥ 50 copies/mL, potential causes of virologic failure should be documented. Assessments should include:

- Review treatment adherence with subject and/or parent/guardian
- Review of AEs and concomitant medications
- Comorbidities (eg, active substance abuse, depression, other intercurrent illnesses)

If virologic rebound is confirmed at the scheduled or unscheduled visit, and the HIV-1 RNA value is ≥ 400 copies/mL, the blood samples from the confirmation visit will be used for HIV-1 genotype/phenotype testing.

If genotype/phenotype resistance to study drug is documented, study drugs should be discontinued.

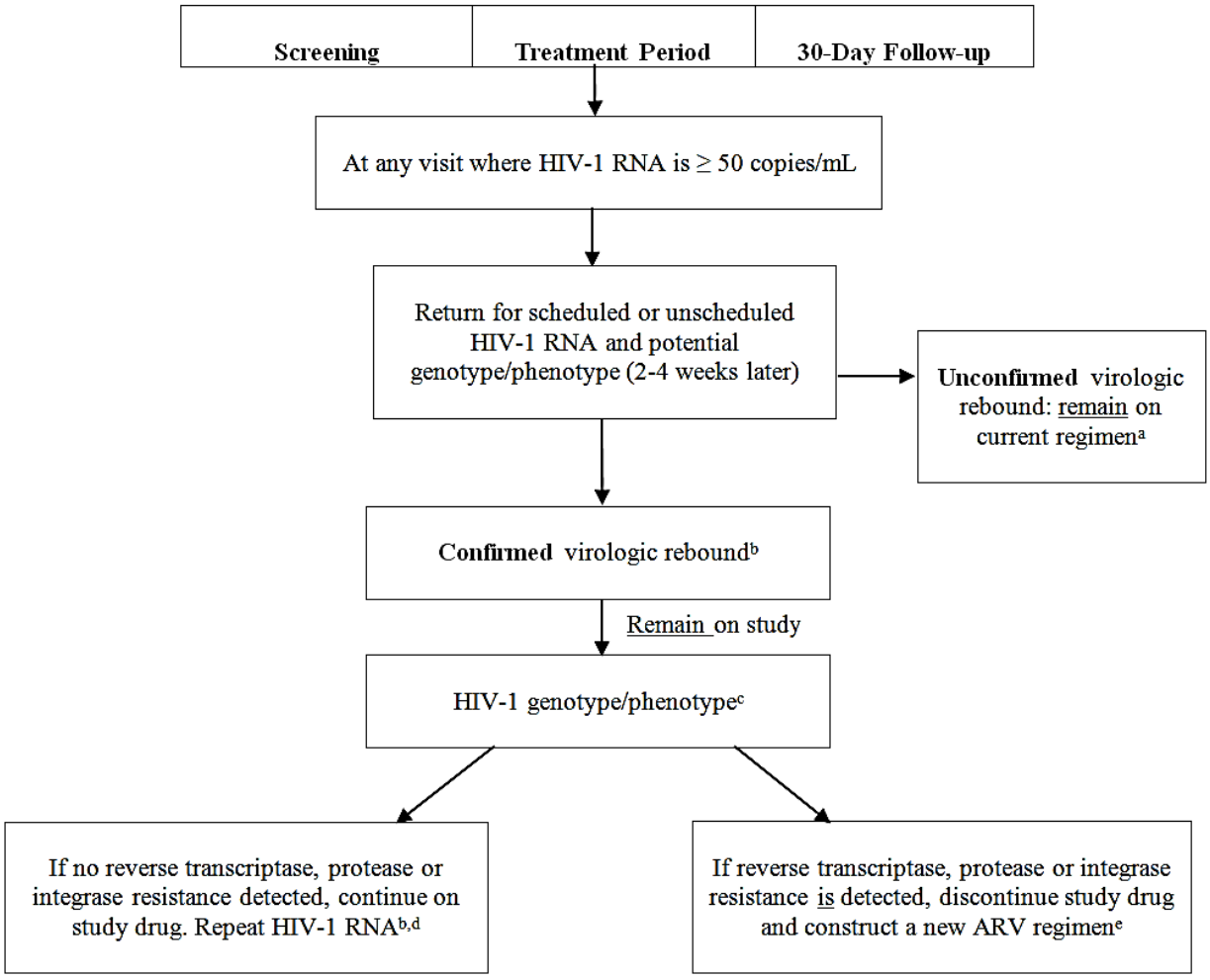
If no resistance is detected from genotype/phenotype testing, subject may remain on study drug and the HIV-1 RNA testing should be repeated (2-4 weeks from the date of confirmed test with viral load ≥ 50 copies/mL) until <50 copies/mL is achieved or the subject discontinues.

Subjects experiencing virologic failure due to emergent resistance on study, but whose virus remains sensitive to FTC and TFV will be permitted to switch to a new fully active 3rd ARV agent and remain on their F/TAF-containing regimen. Subjects unable to tolerate current 3rd agents due to clinically significant toxicities will be permitted to switch after consultation with the medical monitor to a new fully active 3rd ARV agent and remain on their F/TAF-containing regimen.

Investigators should carefully evaluate the benefits and risks of remaining on study drug for each individual subject and document this assessment in the on site medical record. Investigators who opt to discontinue study drugs for an individual subject must discuss with the Gilead Medical Monitor prior to study drug discontinuation.

Please refer to Figure 6-1 for the management of subjects who meet the criteria for virologic rebound.

Figure 6-1. Virologic Rebound Schema



a If virologic rebound is not confirmed, the subject will remain on their current regimen
b If virologic rebound is confirmed, and the HIV-1 RNA is ≥ 400 copies/mL, the HIV-1 genotype and phenotype (reverse transcriptase and protease) will be analyzed
c Based on the results of the genotype/phenotype assays, the subject will remain on study drugs, or study drugs will be discontinued. If genotyping/phenotyping fails, a new ARV regimen may be configured at the discretion of the Investigator
d If no resistance detected, HIV-1 RNA will be repeated (2-4 weeks later) until < 50 copies/mL is achieved or the subject discontinues. Investigator is to review and discuss study drug continuation/discontinuation options with Medical Monitor prior to study drug discontinuation
e A new ARV regimen will be configured, at the Investigator's discretion, and the subject will remain in the study

6.10.1. Subjects with ≥ 400 copies/mL of HIV-1 in Absence of Confirmed Virologic Failure

Subjects may also be analyzed for resistance that does not meet the virologic failure criteria. Subjects who have HIV-1 RNA ≥ 400 copies/mL at Weeks 24 or 48 or the last visit while receiving study drugs (within 72 hours of discontinuation of study treatment) will be analyzed for resistance.

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 7.6.1)
- 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 (e.g., 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 (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 as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (e.g., anemia), not the laboratory result (i.e., decreased hemoglobin).

For specific information on handling of clinical laboratory abnormalities in this study, please refer to Appendix 3.

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified sub-investigator is responsible for assessing the relationship to IMP 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 (e.g., 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 (e.g., 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 (e.g., venipuncture)

7.2.2. Assessment of Severity

Severity should be recorded and graded according to the GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 4). For adverse events associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

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

Requirements for Collection Prior to Study Drug Initiation

After informed consent, but prior to initiation of study medication, the following types of events should be reported on the case report form (CRF/eCRF):

- all serious adverse events (SAEs)
- adverse events related to protocol-mandated procedures.

Adverse Events

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

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

Serious Adverse Events

All SAEs, regardless of cause or relationship, that occurs after the subject first consents to participate in the study (i.e., signing the informed consent) and throughout the duration of the study, including the protocol-required post treatment follow-up period, must be reported to the CRF/eCRF database and Gilead Drug Safety and Public Health (DSPH) as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed. Any SAEs and deaths that occur after the post treatment follow-up visit but within 30 days of the last dose of study IMP, regardless of causality, should also be reported.

All SAEs should be followed up until resolution if possible. If by the last day on study (including the off-study medication follow-up period) the SAE has not resolved, then the SAE 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 SAEs be followed until resolution.

Investigators are not obligated to actively seek SAEs after the follow up 30-day 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 an electronic SAE (eSAE) system using the Electronic Serious Adverse Event Reporting Process detailed below. Gilead will provide training and account information prior to implementing an eSAE system.

- The Serious Adverse Event Paper Reporting Process is to be used only if the EDC System is not available.

Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel will 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, i.e., 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.

- 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, i.e., 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.

Serious Adverse Event Paper Reporting Process

SAEs will be recorded on the serious adverse event paper report form and submitted by faxing or emailing the report form within 24 hours of the Investigator's knowledge of the event to the attention of Gilead DSPH and the medical monitor:

Gilead Sciences Drug Safety Public Health (DSPH):	Fax:	PPD
	E-mail:	PPD
Gilead Sciences Medical Monitor:	Name:	PPD
	Telephone:	PPD
	Mobile Phone:	PPD
	Fax:	PPD
	E-mail:	PPD

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

7.5.1. Toxicity Management

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

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

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

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

7.5.1.1. Management of Bone Toxicity

As there is uncertainty surrounding the clinical significance and management of decreases in bone mineral density for HIV-1 infected children and adolescents, Gilead recommends that any subject who has a DXA scan that demonstrates a decrease from baseline or from the previous visit of ≥ 4% to have a repeat DXA within 7 calendar days to confirm the decrease. If the DXA is confirmed the investigator in consultation with the Gilead medical monitor may decide to discontinue the study drug but keep the subject on the study if feasible.

7.5.2. Grades 1 and 2 Laboratory Abnormality or Clinical Event

Continue investigational medicinal product at the discretion of the Investigator.

7.5.3. Grades 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.

7.5.4. 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 3-4 laboratory abnormality (e.g., CK elevation after strenuous exercise, or triglyceride elevation that is non-fasting or that can be medically managed) or a Grade 3-4 clinical event considered unrelated to investigational medicinal product.

7.5.5. Management of Hyperbilirubinemia in Patients Receiving Ritonavir Boosted Atazanavir

Most patients taking atazanavir sulfate experience asymptomatic elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronyl transferase (UGT). In pediatric clinical trials, 58% of patients experienced Grade 3 to 4 elevations (≥ 3.2 mg/dL) in total bilirubin (Reyataz US Prescribing Information 2013). As subjects in this study who are taking ATV/r as their 3rd ARV agent may frequently have atazanavir-associated hyperbilirubinemia, the management of graded laboratory abnormalities described above in Section 7.5 is not applicable for the management of graded hyperbilirubinemia in these subjects.

However, repeat testing should be done and alternative etiologies (e.g. acute hepatitis B or C) should be sought in the following subjects:

1) In those with elevation in conjugated (direct) bilirubin > 1.5 × ULN (i.e. direct hyperbilirubinemia), regardless of the hyperbilirubinemia grade, liver labs (total bilirubin, direct bilirubin, AST, ALT) should be repeated within 7 days of the Investigator being notified of the elevated bilirubin level and be discussed with the Medical Monitor. Thereafter, the management of a subject who continues to have direct bilirubin > 1.5 × ULN, which is deemed as clinically not significant, should be followed according to the clinical judgment of the Investigator.

2) In those with hepatic transaminase elevation, the graded AST or ALT abnormalities should be managed according to Section 7.5

Dose modification of atazanavir sulfate is not permitted. Subjects who experience unacceptable jaundice/scleral icterus due to atazanavir-associated hyperbilirubinemia can be discontinued from the study at the discretion of the Investigator.

7.6. Special Situations Reports

7.6.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, 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.

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

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

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

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labeling (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.

7.6.2. Instructions for Reporting Special Situations

7.6.2.1. Instructions for Reporting Pregnancies

The Investigator should report all pregnancies in the female subjects that are identified after initiation of study medication and throughout the study, including the post study drug follow-up period, to Gilead DSPH using the pregnancy report form within 24 hours of becoming aware of the pregnancy. Refer to Section 7.6.2 and 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 (e.g., a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 7.3. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead DSPH.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead DSPH 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: PPD and Fax: PPD

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

Refer to Appendix 5 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Recommendations.

7.6.2.2. Reporting Other Special Situations

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

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

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

Refer to Section 7.6.2 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.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objectives of this study are:

- To evaluate the PK of TAF in HIV-1 infected children and adolescents virologically suppressed on 2-NRTI-containing regimen,
- To evaluate the safety and tolerability of F/TAF through Week 24

The secondary objectives of this study are:

- To evaluate the PK of TFV and FTC
- To evaluate the safety, tolerability, and efficacy of F/TAF through Week 48.

8.1.2. Primary Endpoints

The primary endpoints are:

- The PK parameter AUC_{tau} for TAF
- Incidence of treatment-emergent SAEs and all treatment-emergent adverse events through Week 24

8.1.3. Secondary Endpoints

The secondary endpoints are:

- PK parameters of C_{max}, C_{last}, Cl/F, and V_z /F for TAF, AUC_{tau}, C_{max}, and C_{tau} for FTC and TFV
- Incidence of treatment-emergent SAEs and all treatment-emergent adverse events through Week 48
- The percentage of subjects with HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 as defined by the US FDA-defined snapshot algorithm
- The change from baseline in CD4+ cell count (cells/μL) and CD4+ percentage at Weeks 24 and 48
- The palatability and acceptability of the age-appropriate F/TAF formulation

CCI [redacted]

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. All Enrolled

The all enrolled analysis set includes all subjects who are enrolled into the study.

All enrolled analysis set is the primary analysis set for by-subject listings.

8.2.1.2. Efficacy

8.2.1.2.1. Full Analysis Set

The full analysis set (FAS) will include all subjects who are enrolled in the study and have received at least one dose of study medication.

8.2.1.3. Safety

8.2.1.3.1. Safety Analysis Set

The safety analysis set will include all subjects who are enrolled in the study and have received at least one dose of study medication.

8.2.1.4. DXA

8.2.1.4.1. Total Body Less Head DXA Analysis Set

The total body less head DXA analysis set will include all subjects who (1) are enrolled in the study, (2) have received at least one dose of study medication, and (3) have non-missing total body less head BMD value for the baseline visit.

8.2.1.4.2. Spine DXA Analysis Set

The spine DXA analysis set will include all subjects who (1) are enrolled in the study, (2) have received at least one dose of study medication and (3) have non-missing spine BMD value for the baseline visit.

8.2.1.5. Pharmacokinetics

8.2.1.5.1. IPK Analysis Set

The IPK analysis set will include all subjects who (1) are enrolled in Cohort 1 or Part A of Cohorts 2 (each group), 3, and 4 for IPK evaluation, (2) have received at least one dose of study medication and (3) have at least 1 non-missing PK concentration data for any analyte of interest (e.g., FTC, TAF, and TFV). The IPK analysis set will be used for analyses of intensive PK analytes of TAF, TFV, and FTC.

8.2.1.5.2. PK Analysis Set

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

8.2.1.5.3. PBMC PK Analysis Set

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

8.3. Data Handling Conventions

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

8.4. Demographic Data and Baseline Characteristics

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

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

Baseline data including body weight, height/length, body mass index, HIV-1 infection, and enrollment distribution will be summarized.

8.5. Efficacy Analysis

Efficacy endpoints results from each group or cohort will be descriptive in nature.

8.5.1. Primary Analysis

The primary efficacy endpoint is the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 24 as defined by the US FDA-defined snapshot algorithm using the full analysis set (FAS).

Virologic outcomes will be summarized using frequency counts and percentages. The 95% CI for the percentage estimate for each group or cohort will be constructed using the Exact method.

8.5.2. Secondary Analyses

The percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as defined by the US FDA-defined snapshot algorithm will be summarized in the same manner as the primary efficacy endpoint.

The change from baseline in CD4+ cell count and CD4+ percentage will be summarized by visit, group, and cohort using descriptive statistics.

8.6. Safety Analysis

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

All safety data collected on or after the date that the study drug was first administered up to the date of last dose of study drug plus 30 days, unless specified otherwise, will be summarized by group and cohort. Data for the pretreatment period and the period post the date of last dose of study drug plus 30 days will be included in data listings.

Safety results from each group and cohort will be descriptive in nature. F/TAF results from all cohorts will be combined to describe the overall safety profile of F/TAF in subjects 1 month to < 18 years of age.

8.6.1. Extent of Exposure

A subject's extent of exposure to study drug will be generated from the study drug administration data. 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. Exposure data will be summarized by group, cohort, and overall. Dosing information for individual subjects will be listed.

8.6.2. Adverse Events

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

Treatment-emergent AEs are events that meet one of the following criteria up to 30 days after the permanent discontinuation of the study drug:

- Events with onset dates on or after the first dose date of study drug,
- Events that result in permanent study drug discontinuation.

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

On an ongoing basis adverse events will be reviewed for events that might meet the definition of Category C events that are indicative of an AIDS-Defining Diagnoses. The Gilead medical personnel will review the possible Category C events and approve the events that meet the definition. Those events that do meet the Category C definition of an AIDS-Defining Diagnosis will be listed. A listing of Category C, AIDS-Defining Diagnosis can be found in Appendix 6.

8.6.3. Laboratory Evaluations

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

Graded laboratory abnormalities will be defined using the grading scheme defined in Grading of laboratory abnormalities provided in Appendix 4.

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

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

8.6.4. Bone Mineral Density

CCI [redacted] Z-scores (standard Z-scores and adjusted Z-scores) for spine and total body less head BMD and change from baseline in Z-scores will also be summarized by visit, group and cohort. The adjustment method will be specified in the Statistical Analysis Plan.

8.6.5. Bone and Renal Safety Evaluations

Selected bone safety tests, including BsAP, P1NP, CTX, PTH, 1,25-OH vitamin D, and 25-OH vitamin D, will be summarized by visit using descriptive statistics.

For all subjects in all cohorts, selected renal safety tests, including retinol binding protein, and beta-2-microglobulin, will be summarized by visit, group, and cohort using descriptive statistics.

8.6.6. Tanner Stage Assessment

The Tanner stage assessment score will be summarized by study visit, group, and cohort.

8.6.7. Acceptability and Palatability

Acceptability and palatability will be summarized by study visit, group, and cohort.

8.6.8. Other Safety Evaluations

Weight and height/length will be summarized by visit. Safety ECGs will be summarized. Number and percentage of subjects with abnormal safety ECG will be summarized by visit, group, and cohort.

8.7. Pharmacokinetic Analysis

The concentration data of TAF, FTC, and TFV (if applicable) over sampling time will be listed and summarized using descriptive statistics by group and cohort. PK parameters (e.g., AUC_{tau}, AUC_{last}, C_{max}, T_{max}, C_{last}, T_{last}, C_{tau}, λ_z, apparent CL, apparent V_z, and $T_{½}$) will be listed and summarized for analytes TAF, FTC, and TFV (as applicable) using descriptive statistics (e.g., sample size, arithmetic mean, geometric mean, coefficient of variation %, standard deviation, median, Q1, Q3, minimum, and maximum) by group and cohort. Plasma concentrations over time will be plotted in semilogarithmic and linear formats as mean ± standard deviation, and median (Q1, Q3).

TAF exposure PK parameter (i.e., AUC_{tau}) achieved in pediatric subjects from Cohort 1 and Part A of Cohorts 2 (Groups 1 and 2), 3, 4 will be compared to historical adult data (ie, GS-US-311-1089).

An analysis of variance will be carried out for log-transformed TAF AUC_{tau} as a primary parameter while other pharmacokinetic parameters such as C_{max} will be explored. TAF data from each cohort will be compared to Study GS-US-311-1089 adult population PK TAF data by dose level and type of boosted PI (eg, ATV/r or other PIs/r) if applicable. If the lower bound of the 90% CI of the geometric mean ratio (pediatric subjects vs adult subjects) is above 70% for TAF AUC_{tau}, the TAF dose will be confirmed.

In addition, the 95% CI of the geometric mean estimate of apparent CL and apparent V_z of TAF will be provided.

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8.8. Acceptability and Palatability

Acceptability and palatability for the age-appropriate F/TAF FDC formulation will be summarized. Treatment adherence will also be summarized.

8.9. Sample Size

Cohort 1: Twenty-five subjects from Cohort 1 in the TAF treatment arm will provide at least 90% power to target a 95% confidence interval within 60% and 140% of the geometric mean estimate of apparent CL and apparent V_z of TAF, respectively, assuming a standard deviation of 0.60 for CL and 0.58 for V_z (natural log scale) estimated from Study GS-US-292-0106 Cohort 1 Part A.

Cohort 2 (Group 1) Part A: At least 10 subjects on boosted ATV + F/TAF and 6 subjects on boosted LPV or DRV + F/TAF, compared with the population PK data from 44 adult subjects on boosted ATV + F/TAF and 87 adult subjects on boosted LPV or DRV + F/TAF in Study GS-US-311-1089, respectively, will each provide at least 80% power to show the lower bound of a 90% CI of geometric mean ratio (pediatric subjects vs. adult subjects) greater than 70% for AUC_{tau} of TAF, assuming that the expected geometric mean ratios of TAF AUC_{tau} between pediatric subjects and adult subjects are equal to 1 and the standard deviations are 0.40 (with boosted ATV + F/TAF) and 0.33 (with boosted LPV or DRV + F/TAF) ng*hr/mL for TAF AUC_{tau} (natural log scale) estimated from the population PK data in Study GS-US-311-1089.

Part A of Cohorts 2 (Group 2), 3, and 4: At least 10 subjects on boosted ATV + F/TAF and 7 subjects on any other third agent + F/TAF in each group or cohort, compared with the population PK data from the 292 adults on any third agent + DVY in Study GS-US-311-1089, will provide 90% power to show the lower bound of a 90% CI of geometric mean ratio (pediatric subjects vs. adult subjects) greater than 70% for AUC_{tau} of TAF, assuming that the expected geometric mean ratio of TAF AUC_{tau} between pediatric subjects and adult subjects is equal to 1 and the standard deviation is 0.48 ng*hr/mL for TAF AUC_{tau} (natural log scale) estimated from the population PK data in Study GS-US-311-1089.

A total of at least 100 subjects receiving F/TAF from Cohort 1, and Parts A and B of Cohort 2 (Groups 1 and 2), Cohort 3, and Cohort 4 combined will provide reasonable assessment of safety through Week 48 in pediatric subjects.

Sample size and power calculations were made using the statistical software package nQuery Advisor (Version 7.0) and R.

8.10. Data Monitoring Committee

An external multidisciplinary independent data monitoring committee (IDMC) will review the progress of the study and perform interim reviews of safety, efficacy and PK data and provide recommendation to Gilead 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 IDMC's specific activities will be defined in an approved charter, which will define the IDMC's membership, conduct and meeting schedule.

While the IDMC 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.

8.11. Analysis Schedule

Cohort 1

The Week 48 analysis of efficacy and safety will be conducted after the last subject completes Week 48 visit or prematurely discontinue from the study drug. Efficacy and safety endpoints at Week 24 for Cohort 1 will also be analyzed at the Week 48 analysis. A PK analysis will also be performed at the Week 48 analysis.

Cohorts 2, 3 and 4

A PK analysis will be performed after all the subjects enrolled in Part A complete the IPK evaluation within each group (Cohort 2) or each cohort (Cohorts 3 and 4). After the confirmation of TAF dose and TAF safety acceptance among the subjects in Part A, enrollment in Part B will be initiated.

The Week 24 analysis of efficacy and safety will be conducted after the last subject completes Week 24 visit or prematurely discontinue from the study drug within each group (Cohort 2) or cohort (Cohorts 3 and 4). The Week 48 analysis of efficacy and safety will be conducted after the last subject completes Week 48 visit or prematurely discontinue from the study drug within each group (Cohort 2) or cohort (Cohorts 3 and 4).

Final analysis will be performed after all subjects complete the study or prematurely discontinue from the study.

8.12. Endpoint Adjudication Committee

No formal endpoint adjudication committee is planned for this 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 Part 312, Subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR Part 50, and 21 CFR Part 56.

The investigator and all applicable subinvestigators will comply with 21 CFR, Part 54, providing documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug under study. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

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

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an institutional review board or independent ethics committee. 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/ICE detailing any modifications made to the protocol or any accompanying material to be provided to the subject after initial approval, with the exception of those necessary to reduce immediate risk to study subjects.

9.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must use the most current or approved consent form for documenting written

informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by local requirements.

9.1.4. Confidentiality

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

The investigator agrees that all information received from Gilead, including but not limited to the 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, and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

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

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria, i.e., history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Documentation of the reason(s) a consented subject is not enrolled

- Participation in study (including study number);
- Study discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of IMP, including dates of dispensing and return;
- Record of all 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 (i.e., 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. The eCRF should capture the data required per the protocol schedule of events and procedures. All eCRFs 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.

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

The study monitor will provide instructions for return to the designated disposal site. 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, 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 in accordance with local requirements and receive documented 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. Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

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

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

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

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

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

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, e.g. attendance at Investigator's Meetings. If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical trial payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the accuracy of the data recorded in the 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.

9.3.3. Access to Information for Auditing or Inspections

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

9.3.4. Study Discontinuation

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

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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, Open-Label, Multi-Cohort Switch Study to Evaluate Emtricitabine/Tenofovir Alafenamide (F/TAF) in HIV-1 Infected Children and Adolescents Virologically Suppressed on a 2-NRTI-Containing Regimen

GS-US-311-1269, Amendment 2, 02 August 2017

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

PPD

PPD

03 Aug 2017
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

Study Procedure	Screen[c]	Baseline/ Day 1[d]	End of Week[a]								CCI	30 Day Follow-up[e]	ESDD[f]
			1	2	4	8	12	24	36	48			
Informed Consent/Assent	X												
Medical History[g]	X												
Concomitant Medications	X	X	X	X	X	X	X	X	X	X		X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X		X	X
Complete Physical Exam	X	X						X		X			X
Symptom-Directed Physical Exam[i]			X	X	X	X	X		X			X	
12-Lead ECG (performed supine)	X												X
Vital Signs	X	X	X	X	X	X	X	X	X	X		X	X
Weight and Height/Length	X	X	X	X	X	X	X	X	X	X		X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X		X	X
Urine Chemistry		X		X	X	X	X	X		X			X
Selected Renal Safety Tests[k]		X		X	X	X	X	X		X			X[l]
CCI													
Serum Pregnancy Test[m]	X												
Urine Pregnancy Test[n]		X	X	X	X	X	X	X	X	X		X	X
Chemistry Profile	X	X	X	X	X	X	X	X	X	X		X	X
Metabolic Assessments		X						X		X			
Estimated GFR	X	X	X	X	X	X	X	X	X	X		X	X
Hematology Profile	X	X	X	X	X	X	X	X	X	X		X	X
Plasma HIV-1 RNA	X	X	X	X	X	X	X	X	X	X		X	X

Study Procedure	Screen[c]	Baseline/ Day 1[d]	End of Week[a]								CCI	30 Day Follow-up[e]	ESDD[f]
			1	2	4	8	12	24	36	48			
CD4+ Cell Count	X	X	X	X	X	X	X	X	X	X		X	X
CCI													
Whole Blood Sample Storage		X											
Serum Storage Sample												X	X
HCV Serology[p]	X												
HBV Serology	X												
Enrollment[q]		X											
Cohort 1 Dispense Diary Cards[r]			X										
Cohorts 2, 3, & 4 Dispense Diary Cards[r]			X	X									
Single Random PK Sample[s]			X					X					
Cohorts 1 and 2 Fasted Prior to Visit		X		X	X	X	X	X		X			
Cohort 1 IPK Sampling[t]				X									
Cohort 2 Part A IPK Sampling[t]				X[t]	X[t]								
Cohort 1 Palatability and Acceptability Assessment[u]				X									
Cohort 2 Part A Palatability and Acceptability Assessment				X	X								
Single Observed Dosing PK Sample[v]					X		X						
Trough PK Sample[s,w]						X							
PBMC[s,x]						X							
DXA Scan (spine & total body)		X						X		X		X[y]	X[y]

Study Procedure	Screen[c]	Baseline/ Day 1[d]	End of Week[a]								CCI	30 Day Follow-up[e]	ESDD[f]
			1	2	4	8	12	24	36	48			
Cohort 1 Serum Bone Safety Tests[z]		X			X		X	X		X			X[aa]
Cohorts 2, 3, and 4 Serum Bone Safety Tests[z]		X				X	X	X		X			X[aa]
Tanner Stage Assessment[bb]		X						X		X			
In-Clinic Dosing				X	X	X	X						
Study Drug Dispensation		X			X	X	X	X	X	X			
Study Drug Accountability			X	X	X	X	X	X	X	X			X

a All study visits are to be scheduled relative to when the Baseline/Day 1 visit was completed. All study visits through Week 8 are to be completed within ± 2 days of the protocol-specified visit date. Visits between Week 12 through Week 48 are to be completed within ± 4 days of the protocol-specified visit date, unless otherwise specified.

[redacted]

c All screening evaluations are to be completed within 35 days prior to Baseline/Day 1 Visit.

d Subjects will be dispensed study drug on the Baseline/Day 1 Visit. Initiation of treatment with the study drug must take place within 24 hours after the Baseline/Day 1 visit. F/TAF will be provided by the Sponsor unless prohibited by local regulations or upon request by the subject due to insurance restrictions.

e 30 Day Follow-Up only required for CCI [redacted] those subjects who permanently discontinue study drug and do not continue in the study through at least one subsequent visit after the Early Study Drug Discontinuation (ESDD) Visit. For the purpose of scheduling a 30-Day Follow-Up Visit, a ± 6 days window may be used.

f Early Study Drug Discontinuation visit to occur within 72 hours of last dose of study drug. Subjects will be asked to continue attending the scheduled study visits through Week 48 even if the subject discontinues study drug.

g Medical history should include a history of HIV-1 disease-related events, ongoing medications within 30 days of Screening, and all information available on historical genotypes.

[redacted]

i Symptom-directed physical examination, as needed.

[redacted]

k Renal safety tests assessments will be collected fasted for Cohorts 1 and 2. If the subject has not fasted prior to the visit the subject must return within 72 hours in a fasted state to collect urine for renal safety tests.

l Required for ESDD visit if last test was > 12 weeks from ESDD visit.

m Females of childbearing potential in Cohorts 1 and 2 only. Performed at screening and anytime during the study to confirm a positive urine pregnancy test.

n Females of childbearing potential in Cohorts 1 and 2 only. Positive urine pregnancy tests anytime during the study will be confirmed with a serum test.

[redacted]

p If the antibody test result is positive, HCV RNA test will be performed to confirm HCV viremia.

q Assignment of the subject's enrollment number may occur up to 7 days prior to the Baseline/Day 1 visit.

r Diary Cards will be dispensed at Week 1 for all subjects in Cohort 1 to record administration of study drugs and their 3rd ARV agent for at least 3 days prior to the IPK visit at the Week 2 visit. Diary Cards will be dispensed at Week 1 or Week 2 for all subjects in Part A of Cohorts 2, 3, and 4 to record administration of study drugs and their 3rd ARV agent for at least 3 days prior to the IPK visit that is to occur during the Week 2 or 4 visit, or within 7 after the completion of the Week 2 or Week 4 visit. Diary Cards are to be collected and reviewed for protocol compliance prior to in-clinic dosing and IPK sampling. If the subject has already dosed or is not fasted prior to the IPK evaluation visit refer IPK instructions in Section 6.3 for details on how to proceed.

s Subjects are allowed to take study drug at approximately the same time each day however at the time of the single random PK, trough PK, or PBMC sampling they are required to report the time of the last dose.

t IPK will occur during the Week 2 visit for subjects in Cohort 1 and at either the Week 2 or Week 4 visit, or within 7 days after the completion of Week 2 or Week 4 visits, for subjects in Cohort 2 Part A. For the purpose of scheduling the IPK visit, a +7 day window may be used. Subject dosing diary cards are to be collected and reviewed prior to in-clinic dosing and IPK sampling.

u For Cohort 1, palatability will be assessed 30 - 60 minutes after study drug dosing for all subjects undergoing IPK sampling at Week 2. Acceptability will be assessed 30 - 60 minutes after study drug dosing for active subjects at the next study visit immediately following approval of this protocol at the site.

v A single observed dosing PK sample will be collected at Weeks 4 and 12 at any time between 15 min to 4 hours post observed in-clinic dose. For subjects in Cohort 2 Part A, a single observed dosing PK sample does not need to be collected at Week 4 if IPK is collected at the Week 4 visit.

w For subjects in all Cohorts a trough PK sample will be collected during the Week 8 visit at 0 hours (pre-dose, ≤ 30 minutes prior to dosing) will be collected.

x For subjects in Cohorts 1 and 2, PBMC collection will be performed at the Week 8 visit only at study sites that can perform PBMC processing. For subjects in Cohorts 3 and 4, PBMC collection schedule will be specified in a future protocol amendment. All PBMC blood samples will be collected at 0 hours (≤ 30 minutes pre-dose).

y DXA scan to be performed at the 30 Day Follow-up visit or the ESDD visit if the last scan was acquired > 12 weeks from the date of the ESDD Visit. DXA scan can occur up to 10 days after the ESDD visit date.

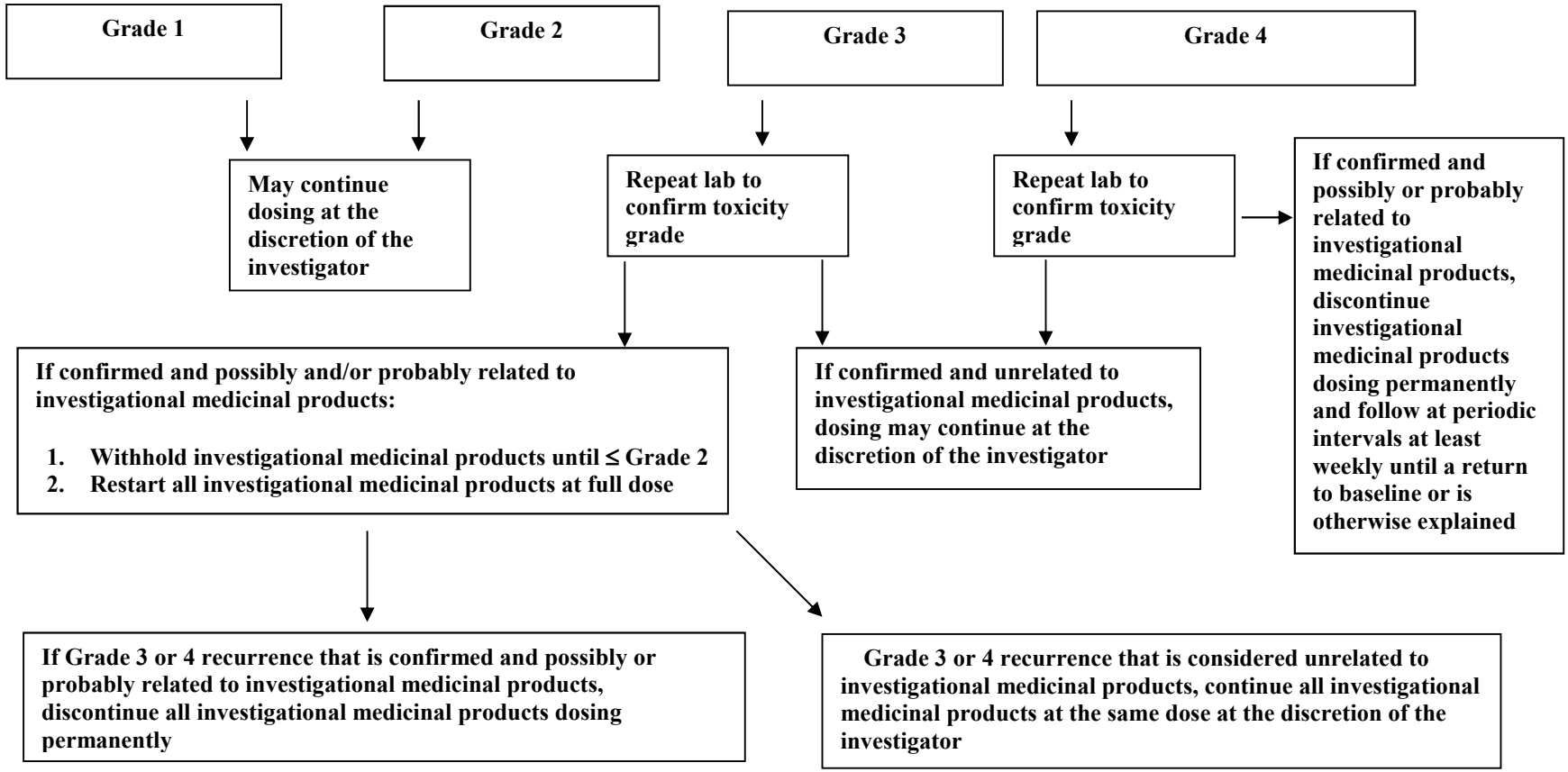
z If the subject has not fasted prior to the blood draw for serum bone safety tests visit may continue however the subject must return within 72 hours after completion of the visit in a fasted state to draw blood for serum bone safety tests.

aa Serum bone safety test is required at ESDD visit if last test was > 12 weeks from ESDD visit.

bb Tanner assessments will be performed at Baseline/Day1, Weeks 24 and 48 CCI [redacted]

CCI [redacted]

Appendix 3. Management of Clinical and Laboratory Adverse Events



Appendix 4. 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)	1000 to 1300/mm^3	750 to < 1000/mm^3	500 to < 750/mm^3	< 500/mm^3
Adult and Pediatric, > 7 Days	1.00 to 1.30 GI/L	0.75 to < 1.00 GI/L	0.50 to < 0.75 GI/L	< 0.50 GI/L
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

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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 2.00 GI/L to 2.50 GI/L	1,500 to < 2,000/mm^3 1.50 to < 2.00 GI/L	1000 to < 1,500/mm^3 1.00 to < 1.50 GI/L	< 1000/mm^3 < 1.00 GI/L
Hypofibrinogenemia	100 to 200 mg/dL 1.00 to 2.00 g/L	75 to < 100 mg/dL 0.75 to < 1.00 g/L	50 to < 75 mg/dL 0.50 to < 0.75 g/L	< 50 mg/dL < 0.50 g/L
Hyperfibrinogenemia	> ULN to 600 mg/dL > ULN to 6.0 g/L	> 600 mg/dL > 6.0 g/L	— —	— —
Fibrin Split Product	20 to 40 µg/mL 20 to 40 mg/L	> 40 to 50 µg/mL > 40 to 50 mg/L	> 50 to 60 µg/mL > 50 to 60 mg/L	> 60 µg/mL > 60 mg/L
Prothrombin Time (PT)	> 1.00 to 1.25 × ULN	> 1.25 to 1.50 × ULN	> 1.50 to 3.00 × ULN	> 3.00 × ULN
International Normalized Ratio of prothrombin time (INR)	1.1 to 1.5 x ULN	>1.5 to 2.0 x ULN	>2.0 to 3.0 x ULN	>3.0 x ULN
Activated Partial Thromboplastin Time (APTT)	> 1.00 to 1.66 × ULN	> 1.66 to 2.33 × ULN	> 2.33 to 3.00 × ULN	> 3.00 × ULN
Methemoglobin	5.0 to 10.0%	> 10.0 to 15.0%	> 15.0 to 20.0%	> 20.0%

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** **Infant, < 1 Month**	 55 to 64 mg/dL 3.03 to 3.58 mmol/L 50 to 54 mg/dL 2.8 to 3.0 mmol/L	 40 to < 55 mg/dL 2.20 to < 3.03 mmol/L 40 to < 50 mg/dL 2.2 to < 2.8 mmol/L	 30 to < 40 mg/dL 1.64 to < 2.20 mmol/L 30 to < 40 mg/dL 1.7 to < 2.2 mmol/L	 < 30 mg/dL < 1.64 mmol/L < 30 mg/dL < 1.7 mmol/L
Hyperglycemia, Nonfasting	116 to 160 mg/dL 6.42 to 8.91 mmol/L	> 160 to 250 mg/dL > 8.91 to 13.90 mmol/L	> 250 to 500 mg/dL > 13.90 to 27.79 mmol/L	> 500 mg/dL > 27.79 mmol/L
Hyperglycemia, Fasting	110 to 125 mg/dL 6.08 to 6.96 mmol/L	>125 to 250 mg/dL >6.96 to 13.90 mmol/L	>250 to 500 mg/dL >13.90 to 27.79 mmol/L	>500 mg/dL >27.79 mmol/L
Hypocalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥ 7 Days** **Infant, < 7 Days**	7.8 to 8.4 mg/dL 1.94 to 2.10 mmol/L 6.5 to 7.5 mg/dL 1.61 to 1.88 mmol/L	7.0 to < 7.8 mg/dL 1.74 to < 1.94 mmol/L 6.0 to < 6.5 mg/dL 1.49 to < 1.61 mmol/L	6.1 to < 7.0 mg/dL 1.51 to < 1.74 mmol/L 5.5 to < 6.0 mg/dL 1.36 to < 1.49 mmol/L	< 6.1 mg/dL < 1.51 mmol/L < 5.5 mg/dL < 1.36 mmol/L
Hypercalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥ 7 Days** **Infant, < 7 Days**	>ULN to 11.5 mg/dL >ULN to 2.88 mmol/L 11.5 to 12.4 mg/dL 2.86 to 3.10 mmol/L	> 11.5 to 12.5 mg/dL > 2.88 to 3.13 mmol/L > 12.4 to 12.9 mg/dL > 3.10 to 3.23 mmol/L	> 12.5 to 13.5 mg/dL > 3.13 to 3.38 mmol/L > 12.9 to 13.5 mg/dL > 3.23 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L > 13.5 mg/dL > 3.38 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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** **Infant, ≤ 14 Days** (non-hemolytic) **Infant, ≤ 14 Days** (hemolytic)	 > 1.0 to 1.5 × ULN NA NA	 > 1.5 to 2.5 × ULN 20.0 to 25.0 mg/dL 342 to 428 µmol/L NA	 > 2.5 to 5.0 × ULN > 25.0 to 30.0 mg/dL > 428 to 513 µmol/L 20.0 to 25.0 mg/dL 342 to 428 µmol/L	 > 5.0 × ULN > 30.0 mg/dL > 513 µmol/L > 25.0 mg/dL > 428 µmol/L
Blood Urea Nitrogen	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Hyperuricemia	>ULN to 10.0 mg/dL >ULN to 597 µmol/L	> 10.0 to 12.0 mg/dL > 597 to 716 µmol/L	> 12.0 to 15.0 mg/dL > 716 to 895 µmol/L	> 15.0 mg/dL > 895 µmol/L
Hypouricemia	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

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
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) **Pediatric >2 to <18 years**	130 to 160 mg/dL 3.35 to 4.15 mmol/L 110 to 130 mg/dL 2.84 to 3.37 mmol/L	>160 to 190 mg/dL >4.15 to 4.92 mmol/L >130 to 190 mg/dL >3.37 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L > 190 mg/dL >4.92 mmol/L	NA NA
Hypercholesterolemia (Fasting) **Pediatric < 18 Years**	200 to 239 mg/dL 5.16 to 6.19 mmol/L 170 to 199 mg/dL 4.39 to 5.15 mmol/L	> 239 to 300 mg/dL > 6.19 to 7.77 mmol/L > 199 to 300 mg/dL > 5.15 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L > 300 mg/dL > 7.77 mmol/L	NA NA
Creatine Kinase	3.0 to < 6.0 × ULN	6.0 to < 10.0 × ULN	10.0 to < 20.0 × ULN	≥ 20.0 × ULN

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

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
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) **Pediatric ≤ 17 Years** (with repeat testing at same visit)	140–159 mmHg systolic OR 90–99 mmHg diastolic NA	> 159–179 mmHg systolic OR > 99–109 mmHg diastolic 91st–94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	> 179 mmHg systolic OR > 109 mmHg diastolic ≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization (other than ER visit) indicated Life-threatening consequences (e.g., 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 non-urgent intervention indicated	Life-threatening consequences (e.g., 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, e.g., 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, e.g., Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/Embolism	NA	Deep vein thrombosis AND No intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Embolic event (e.g., 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 [e.g., tube feeding or total parenteral nutrition]
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (e.g., 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 (e.g., sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., 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 (e.g., 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 (e.g., 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 (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than ER visit)	Symptomatic AND Hospitalization indicated (other than ER visit)	Life-threatening consequences (e.g., 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 (e.g., 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 (e.g., hypotensive shock)

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

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

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Seizure: (pre-existing) For Worsening of Existing Epilepsy the Grades Should Be Based on an Increase from Previous Level of Control to Any of These Levels	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR infrequent breakthrough seizures while on stable meds in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (e.g., severity or focality)	Seizures of any kind that are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., 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 **Pediatric < 21 Years**	BMD t-score or z-score –2.5 to –1.0 BMD z-score –2.5 to –1.0	BMD t-score or z-score < –2.5 BMD z-score < –2.5	Pathological fracture (including loss of vertebral height) Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences Pathologic fracture causing life-threatening consequences
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions

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 [e.g., 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	Erythema OR Induration of 5 × 5 cm to 9 × 9 cm (or 25–81 × cm^2)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pediatric ≤ 15 Years	Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (e.g., upper arm/thigh)	Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (e.g., upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pruritis Associated with Injection See also Skin: Pruritis (itching—no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 h treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 h treatment	Generalized itching causing inability to perform usual social & functional activities	NA

ENDOCRINE/METABOLIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Lipodystrophy (e.g., 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 (e.g., 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 (e.g., 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 (e.g., myxedema coma)
Lipoatrophy (e.g., 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 (e.g., 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 (e.g., septic shock)

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

Appendix 5. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Pregnancy and Contraception Requirements for Males and Females of Childbearing Potential

The risks of treatment with the study drug during pregnancy have not been evaluated. Pregnancy must be excluded before the start of treatment with study drug and prevented thereafter by reliable contraceptive methods. Pregnancy tests will be performed regularly throughout this study (Refer to Appendix 2). If females are using hormonal agents for contraception, the safety and/or efficacy may be affected by possible drug-drug interaction. However, it is recommended that the hormonal agent be continued and that a non-hormonal method (or methods) be used concurrently.

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.

2) Definition of Female of Childbearing Potential

For the purposes of this study, a female subject of childbearing potential is a nonmenopausal female who has not had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure. A woman who has had a tubal sterilization is considered to be of childbearing potential. This definition also includes a pubertal female who has not yet started menstruating.

A female subject may be considered menopausal in either of the following conditions:

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

- Spontaneous menopause: Permanent cessation of previously occurring menses as a result of ovarian failure with documentation of hormonal deficiency by a certified health care provider. The worldwide mean age of spontaneous menopause is 49.24 (SD 1.73) years

3) Contraceptive Requirements

Female subjects of childbearing potential who engage in intercourse must agree to utilize protocol specified methods of contraception from the screening visit throughout the study period and for 30 days following the last dose of study drug. Male subjects of childbearing potential who engage in intercourse must agree to utilize protocol specified methods of contraception from the enrollment visit throughout the study period and for 30 days following the last dose of study drug.

Female study subjects who are not heterosexually active must provide periodic confirmation of continued abstinence from heterosexual intercourse and regular pregnancy testing while taking any study medication. The investigator will counsel subjects on the protocol specified method(s) for avoiding pregnancy in case the subject chooses to engage in heterosexual intercourse.

Protocol specified contraceptive methods are as follows:

1) a combination of one hormonal method and one barrier method;

2) two barrier methods where one method is the male condom;

3) use of an intrauterine device (IUD) or tubal sterilization;

See Appendix Table 1 below. Acceptable hormonal methods include injectable progesterone, progesterone implants, combination oral contraceptives, transdermal contraceptive patch, and vaginal ring. Acceptable barrier methods include diaphragm with spermicide, cervical cap with spermicide, and the male condom.

Female subjects must use either a hormonal method or a barrier method if the partner has a vasectomy. If a subject has undergone tubal sterilization or has had a Copper T 380A IUD or LNg 20 IUD inserted, no other contraception is needed.

If tubal sterilization is via the Essure procedure, verification of tubal blockage by hysterosalpingogram (HSP) must be performed approximately 3 months after microinsertion. Prior to verification, Essure is not considered a reliable form of contraception and the contraception methods described below must be used. 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.

Female subjects 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 IMP administration.

Appendix Table 1. Protocol Specified Contraceptive Methods

<table>
<tr><th rowspan="2">Methods to Use by Themselves</th><th colspan="2">Combination Methods</th></tr>
<tr><th>Hormone Methods
(choose one and use with a barrier method)</th><th>Barrier Methods
(use both OR choose one and use with a hormone method)</th></tr>
<tr><td rowspan="2">Intrauterine Devices (IUDs)
• Copper T 380A IUD
• LNg 20 IUD

Tubal Sterilization</td><td>Estrogen and Progesterone
• Oral contraceptives
• Transdermal patch
• Vaginal ring
Progesterone
• Injection
• Implant</td><td>• Diaphragm with spermicide
OR
• Cervical cap with spermicide
• Male condom (without spermicide)</td></tr>
<tr><td colspan="2">Partner’s vasectomy must be used with a hormone or barrier method.</td></tr>
</table>

The investigator will counsel all subjects on the most effective method(s) for avoiding pregnancy during the study.

Male subjects must agree to use condoms during heterosexual intercourse and avoid sperm donation while enrolled in the study and for at least 30 days after administration of the last dose of study medication

Use of condoms, except for lambskin, has been proven to decrease the risk of transmission of HIV and other sexually transmitted diseases. The use of spermicide is not recommended if the subject or subject's partner is infected with HIV.

4) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 30 days of last study drug dose.

Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and seek the investigator's advice regarding action required with the study drug immediately.

Instructions for reporting pregnancy and pregnancy outcome are outlined in Section 7.6.2.1.

Appendix 6. Definitions of HIV-1 Related Disease

CDC Classification Systems, Category C: AIDS-Indicator Conditions

- Bacterial pneumonia, recurrent (two or more episodes in 12 months)
- Candidiasis of bronchi, trachea, or lungs
- Candidiasis, esophageal
- Cervical carcinoma, invasive, confirmed by biopsy
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (> 1 month duration)
- Cytomegalovirus disease (other than liver, spleen or nodes)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcers (> 1 month duration), or bronchitis, pneumonitis or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (> 1-month duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt, immunoblastic, or primary central nervous system
- *Mycobacterium avium* complex (MAC) or *Myobacterium kansasii*, disseminated or extrapulmonary
- *Mycobacterium tuberculosis*, pulmonary or extrapulmonary
- *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis jirovecii* (formerly *carinii*) pneumonia (PCP)
- Progressive multifocal leukoencephalopathy (PML)
- *Salmonella* septicemia, recurrent (nontyphoid)

- Toxoplasmosis of brain

- Wasting syndrome caused by HIV (involuntary weight loss > 10% of baseline weight) associated with either chronic diarrhea (two or more loose stools per day for ≥ 1 month) or chronic weakness and documented fever for ≥ 1 month

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Appendix 7. 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.