STATISTICAL ANALYSIS PLAN

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
Name of Test Drug:	Emtricitabine/Tenofovir Alafenamide (F/TAF)
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CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

ABC/3TC	abacavir (ABC)/lamivudine (3TC)
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARV	antiretroviral
AST	aspartate aminotransferase
ATV	atazanavir
ATV/r	ritonavir boosted atazanavir
AUC	area under curve for concentration over time
BIC	bictegravir
B/F/TAF	fixed dose combination of bictegravir (BIC; B) 50 mg / emtricitabine (FTC; F) 200 mg / tenofovir alafenamide (TAF) 25 mg
BLQ	below limit of quantitation
BMD	bone mineral density
BMI	body mass index
BSA	body surface area
CDC	Centers for Disease Control
CDER	Center for Drug Evaluation and Research
CL/F	the apparent oral clearance after administration of the drug: $CL/F = Dose/AUC_{inf}$ where "Dose" is the dose of the drug
CL	volume of plasma cleared of drug per unit time
CI	confidence interval
CPK	creatine phosphokinase
CRF	case report form
CSR	clinical study report
CV	coefficient of variation
DC	study drug discontinuation
DRV	darunavir
DXA	dual-energy X-ray absorptiometry
DSPH	Drug Safety and Public Health
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
$eGFR_{Schwartz}$	estimated glomerular filtration rate calculated using the Schwartz formula
FAS	full analysis set
FDA	Food and Drug Administration
FDC	fixed-dose combination
FTC, F	emtricitabine
GFR	glomerular filtration rate

Gilead	Gilead Sciences, Inc.
GS-9883	bictegravir
h	hour
HBV	hepatitis B Virus
HCV	hepatitis C Virus
HIV-1	human immunodeficiency virus (Type 1)
HDL	high-density lipoprotein
HLGT	high-level group term
HLT	high-level term
IDMC	independent data monitoring committee
IPK	intensive pharmacokinetics
kg	kilogram
LDL	low-density lipoprotein
LLOQ	lower limit of quantitation
LLT	lowest level term
LPV	lopinavir
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
ng	nanogram
NRTI	nucleoside reverse transcriptase inhibitor
PBMC	peripheral blood mononuclear cell
PI	protease inhibitor
PT	preferred term
PK	pharmacokinetics
Q	quartile
Q1	first quartile
Q3	third quartile
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SCr	serum creatinine
SD	standard deviation
SE	standard error
SMQ	standardized MedDRA query
SOC	system organ class
SQRT	square root, √
TAF	tenofovir alafenamide
TEAE	treatment-emergent adverse events
TFL	tables, figures, and listings
TFV	tenofovir

ULN	upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the clinical study report (CSR) for Study GS-US-311-1269. This SAP is based on the study protocol amendment 2 dated 02 August 2017 and the electronic case report form (eCRF). The SAP will be finalized before database finalization. Any changes made after the finalization of the SAP will be documented in the CSR.

1.1. Study Objectives

The primary objective of this study is as follows:

- 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 F/TAF through Week 24.

The secondary objectives of this study are as follows:

- To evaluate the PK of tenofovir (TFV) and emtricitabine (FTC).

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

1.2. Study Design

This is 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 (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- atazanavir (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:

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.

Study Procedure/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 estimated glomerular filtration rate (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, CCI [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 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 IPK 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 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.

Peripheral Blood Mononuclear Cell (PBMC) collection:

- PBMC collection will be performed at study sites that canperform 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.

The additional details of Schedule of Assessments can be found in Appendix 1.

Test Product, Dose, and Mode of Administration:

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

Cohort	Age Range	Weight Range	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 kg to < 25 kg	120/15
3 (subjects unable to swallow a tablet)	2 to < 6 years	TBD	TBD
4	1 month to < 2 years	TBD	TBD

1.3. Sample Size and Power

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 volume of plasma cleared of drug per unit time (CL) and apparent Vz of TAF, respectively, assuming a standard deviation of 0.60 for CL and 0.58 for Vz (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 lopinavir (LPV) or darunavir (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% confidence interval (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.

2. TYPE OF PLANNED ANALYSIS

2.1. Cohort 1 Interim Analysis

A Cohort 1 Week 48 analysis was planned to be conducted after all subjects in Cohort 1 either complete their Week 48 visit or prematurely discontinue from the study drug. This analysis was not done as this study was not needed to support the new drug application (NDA) for F/TAF for pediatrics.

2.2. Cohort 2 Interim Analysis

A Cohort 2 Week 24 analysis was planned to be conducted after all subjects in Cohort 2 either complete their Week 24 visit or prematurely discontinue from the study drug. This analysis was not done as this study was not needed to support the NDA for F/TAF for pediatrics.

2.3. Analysis for CT.gov

The Food and Drug Administration (FDA) Amendment Act of 2007 requires that the results for the primary endpoint be posted on ClinicalTrials.gov within one year of the last patient last visit of the primary endpoint.

This statistical analysis plan describes the analysis planned to be posted on CT.gov. Only the primary and secondary endpoints are included in this analysis.

2.4. Final Analysis

Final Analysis will be conducted after all subjects (Cohorts 1 and 2) either complete the study or prematurely discontinue from the study. The Cohorts 3 and 4 were not enrolled.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of subjects in each category will be presented; for continuous variables, the number of subjects (n), mean, standard deviation (SD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

By-subject listings will be presented for all subjects in the All Enrolled analysis set unless otherwise specified, and sorted by subject ID number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order within a subject.

In general, age (in years) on the date of the first dose of study drug will be used for analyses and presentation in listings. For enrolled but never dosed subjects, age on the date of enrollment will be used. For screen failures, age on the date the informed consent was signed will be used. If only birth year is collected on the eCRF, "01 January" will be used for the unknown birth day and month for the purpose of age calculation, similarly, if only birth year and month are collected on the eCRF, "01" will be used for the unknown birth day for the purpose of age calculation.

In general, permanent discontinuation of study drug refers to premature discontinuation of study drug or completion of study drug.

3.1. Analysis Sets

Analysis sets define the subjects to be included in an analysis. Analysis sets and their definitions are provided in this section. Subjects included in each analysis set will be determined before data finalization. The analysis set will be included as a subtitle of each table, figure, and listing. A summary of the number and percentage of subjects in each analysis set will be provided.

3.1.1. All Enrolled Analysis Set

The **All Enrolled Analysis Set** will include all subjects who are enrolled into the study. This is the primary analysis set for by-subject listings.

3.1.2. Full Analysis Set

The **Full Analysis Set (FAS)** will include all subjects who (1) are enrolled into the study and (2) have received at least 1 dose of study drug. For the FAS, all efficacy data, including data collected after the last dose of study drug, will be included, unless specified otherwise. This is the primary analysis set for efficacy analyses.

3.1.3. Safety Analysis Set

The **Safety Analysis Set** will include all subjects who (1) are enrolled into the study and (2) have received at least 1 dose of study drug. All the data collected up to 30 days after permanent discontinuation of the study drug will be included in the safety summaries, unless specified otherwise. This is the primary analysis set for safety analyses.

3.1.4. DXA Analysis Set

3.1.4.1. Spine DXA Analysis Set

The spine DXA analysis set will include all subjects who are enrolled and have received at least 1 dose of study drug, and have non-missing spine BMD value at baseline visit.

3.1.4.2. Total Body Less Head DXA Analysis Set

The total body less head DXA analysis set will include all subjects who are enrolled and have received at least 1 dose of study drug, and have non-missing total body less head BMD value at baseline visit.

3.1.5. PK Analysis Sets

The PK analysis set for each analyte of interest will include all subjects who (1) are enrolled into Cohort 1 or Cohort 2 for PK evaluation, (2) have received at least one dose of study medication and (3) have at least 1 non-missing IPK concentration data for that analyte (eg, TAF, TFV, and FTC).

3.2. Subject Grouping

For Cohort 1, subjects will be grouped into 1 treatment group (ie, F/TAF) for efficacy and safety analyses. For Cohort 2, subjects will be grouped into 2 groups: Group 1: Age 6 to < 12 years and weight ≥ 25 kg and Group 2: Age 2 to < 12 years and weight 17 to < 25 kg.

3.3. Strata and Covariates

Not applicable.

3.4. Examination of Subject Subgroups

Not applicable.

3.5. Multiple Comparisons

Not applicable.

3.6. Missing Data and Outliers

3.6.1. Missing Data

A missing datum for a given study analysis window may be due to any of the following reasons:

- A visit occurring in the window but data were not collected or were unusable
- A visit not occurring in the window
- A subject prematurely discontinuing from the study before reaching the window

In general, values for missing data will not be imputed, unless methods for handling missing data are specified.

For missing last dosing date of study drug, imputation rules are described in Section 3.7. The handling of missing or incomplete dates for AE onset is described in Section 7.1.5.2.

3.6.2. Outliers

Outliers will be identified during the data management and data analysis process, but no sensitivity analyses will be done to evaluate the impact of outliers on efficacy or safety outcomes, unless specified otherwise. All data will be included in the analyses.

3.7. Data Handling Conventions and Transformations

Laboratory data that are continuous in nature but are less than the lower limit of quantitation or above the upper limit of quantitation will be imputed as follows:

- A value that is 1 unit less than the limit of quantitation will be used for calculation of descriptive statistics if the datum is reported in the form of "< x" (where x is considered the limit of quantitation). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used for calculation of summary statistics. An exception to this rule is any value reported as < 1 or < 0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used for calculation of summary statistics.
- A value that is 1 unit above the limit of quantitation will be used for calculation of descriptive statistics if the datum is reported in the form of "> x" (where x is considered the limit of quantitation). Values with decimal points will follow the same logic as above.
- The limit of quantitation will be used for calculation of descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the limit of quantitation).

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

Natural logarithm transformation will be used for analyzing concentrations and PK parameters. Concentration and PK parameter values that are below the limit of quantitation (BLQ) will be presented as "BLQ" in the data listing. Values that are BLQ will be treated as 0 at predose time points, and one-half the value of the LOQ at postdose time points for summary purposes.

The following conventions will be used for the presentation of summary and order statistics for PK concentrations:

- If at least 1 subject has a concentration value of BLQ for the time point, the minimum value will be displayed as "BLQ."
- If more than 25% of the participants have a concentration data value of BLQ for a given time point, the minimum and Q1 values will be displayed as "BLQ."
- If more than 50% of the participants have a concentration data value of BLQ for a given time point, the minimum, Q1, and median values will be displayed as "BLQ."
- If more than 75% of the participants have a concentration data value of BLQ for a given time point, the minimum, Q1, median, and Q3 values will be displayed as "BLQ."
- If all participants have concentration data values of BLQ for a given time point, all order statistics (minimum, Q1, median, Q3, and maximum) will be displayed as "BLQ."

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

Study Day 1 is defined as the day when the first dose of study drug F/TAF was taken, as recorded on the Study Drug Administration eCRF form.

Study Days are calculated relative to Study Day 1. For events that occurred on or after the Study Day 1 date, study days are calculated as (visit date minus Study Day 1 plus 1). For events that occurred prior to Study Day 1, study days are calculated as (visit date minus Study Day 1).

Last Dose Date is the earliest of the last dosing dates of F/TAF and the third agent in a subject's study regimen.

For F/TAF, the last dosing date is the latest nonmissing end date recorded on the Study Drug Administration eCRF form with "Study Drug Permanently Withdrawn" box checked for subjects who prematurely discontinued study drug or who completed study drug according to Study Drug Completion eCRF. If the date of last dose is missing (eg, due to lost to follow-up) for subjects who prematurely discontinued study drug or who are still on study drug, the latest of nonmissing study drug start dates and end dates, the clinic visit dates, and the laboratory visit dates excluding the date of 30-day follow-up visit will be used to impute the last dosing date.

The third agent in a subject's existing treatment regimen is the ARV medications (excluding ABC and 3TC) that a subject was taking immediately prior to the first dose date (ie, ARV start date < the first dose date of study drug and ARV end date ≥ the first dose date of study drug 1). The last dosing date of the third agent is recorded on the ARV eCRF form. If the third agent is ongoing, then the last dose date of the study regimen will be the last dosing date of F/TAF.

For an ARV which is marked as current but not ongoing on the ARV eCRF form, if the ARV end date is missing (eg, due to lost to follow-up), the latest of nonmissing study drug start dates and end dates, the clinic visit dates, and the laboratory visit dates excluding the date of 30-day follow-up visit will be used to impute the end date of this ARV.

Baseline value is defined as the last value obtained on or prior to Study Day 1 for all assessments, exept for the BMD data, which is the last value on or prior to Study Day 21.

3.8.2. Analysis Visit Windows

Subject visits might not occur on protocol-specified days. Therefore, for the purpose of analysis, observations will be assigned to analysis windows.

The analysis windows for HIV-1 RNA, CD4 cell count, CD4 %, hemotology, chemistry, and urinalysis laboratory test, $eGFR_{Schwartz}$, vital signs, height, and weight are presented in Table 3-1.

Table 3-1. Analysis Windows for HIV-1 RNA, CD4 cell count, CD4 %, Hematology, Chemistry, and Urinalysis Laboratory Tests, eGFRSchwartz, Vital Signs, Height, and Weight

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 1	7	2	10
Week 2	14	11	21
Week 4	28	22	42
Week 8	56	43	70
Week 12	84	71	126
Week 24	168	127	210
Week 36	252	211	294
Week 48	336	295	378

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The analysis windows for DXA assessments are presented in Table 3-2.

Table 3-2. Analysis Windows for BMD Assessments

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			21
Week 24	168	22	252
Week 48	336	253	420

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3.8.3. Selection of Data in the Event of Multiple Records in an Analysis Visit Window

Depending on the statistical analysis method, single values are required for each analysis window. For example, change from baseline by visit usually requires a single value, whereas a time to event analysis would not require one value per analysis window. When a single value is needed, the following rule(s) will be used.

If multiple nonmissing numeric observations exist in a window, then records will be chosen as follows:

- For baseline, the latest available record on or prior to the first dose date of study drug will be selected. If there are multiple records with the same time or no time recorded on the same day, average will be used for the baseline value, except for HIV-1 RNA (see below).
- For postbaseline visits:

  For CD4 cell count and CD4% data, the record(s) collected on the latest day in the window will be selected for analysis.

  For other numeric observations (ie, except HIV-1 RNA, CD4 cell count, and CD4%), the record(s) collected on the day closest to the nominal day for that visit will be selected. If there are 2 days equidistant from the nominal day, the later day will be selected.

  For any numeric observations except HIV-1 RNA, if there are multiple records on the selected day, the average will be taken.

- For baseline and postbaseline HIV-1 RNA, the latest (considering both date and time) record(s) in the window will be selected. If both "HIV RNA Taqman 2.0" and "HIV RNA Repeat" (ie, the HIV-1 RNA result obtained from an additional aliquot of the original sample) are available with the same collection time, the results from the "HIV RNA Repeat" will be selected for analysis purposes; otherwise, if there are multiple "HIV RNA Taqman 2.0" records with the same collection time, the geometric mean will be taken for analysis purposes.

If multiple valid nonmissing categorical observations exist in a window, records will be chosen as follows:

- For baseline, the last available record on or prior to the first dose date of study drug will be selected. If there are multiple records with the same time or no time recorded on the same day, the value with the lowest severity will be selected (eg, normal will be selected over abnormal).

- For postbaseline visits, the most conservative value within the window will be selected (eg, abnormal will be selected over normal).

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

4.1.1. Subject Enrollment

The number and percentage of subjects enrolled at each country and investigator will be summarized using the safety analysis set.

4.1.2. Subject Disposition

The summary of subject disposition will be provided for all screened subjects. This summary will include the number of subjects screened, screen failure subjects who were not enrolled, subjects who met all eligibility criteria and were not enrolled, subjects enrolled, subjects enrolled but never treated, subjects in the safety analysis set, DXA Analysis set, IPK analysis set, and subjects in the FAS.

In addition, the number and percentage of the subjects in the following categories will be summarized:

For the 48-Week treatment phase (up to Week 48):

- Completed study drug
- Still on study drug
- Prematurely discontinuing study drug prior to Week 48 (with summary of reasons for discontinuing study drug)
- Completed Study
- Still on Study
- Prematurely discontinuing study prior to Week 48 (with summary of reasons for discontinuing study)

- Completed study
- Still on study

[redacted]

The denominator for the percentages of subjects in each category will be the number of subjects in the safety analysis set.

No inferential statistics will be generated. A data listing of reasons for premature study drug/study discontinuation will be provided.

4.2. Extent of Study Drug Exposure

Duration of exposure to study drug will be defined as (the last dose date the first dose date + 1), regardless of temporary interruptions in study drug administration, and will be expressed in weeks using up to 1 decimal place (eg, 4.5 weeks). For the calculation of the duration of exposure to study drug, the data cut date will be used to impute the last dose date for subjects who have not permanently discontinued study drug at the time of the data cut date.

Duration of exposure to study drug will be summarized using descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, and maximum) and as the number and percentage of subjects exposed for specified periods, eg, ≥ 4 weeks (28 days), ≥ 8 weeks (56 days), ≥ 12 weeks (84 days), ≥ 24 weeks (168 days), ≥ 36 weeks (252 days), etc.

Summaries will be provided for subjects in the safety analysis set. No inferential statistics will be provided.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Subject demographic data (eg, age, sex at birth, race, and ethnicity) and baseline characteristics (eg, body weight, weight Z-score, height, height Z-score, body surface area [BSA], body mass index [BMI], and Tanner Stage) will be summarized using descriptive statistics for all subjects in the safety analysis set. The percentage of subjects who reach Tanner Stage 4 or 5 will also be summarized. The sample size, mean, SD, median, Q1, Q3, minimum, and maximum will be provided for continuous data, and the number and percentage of subjects will be provided for categorical data. Age is calculated as age in years at first dose of study drug. The definition of baseline value is provided in Section 3.8.1.

5.2. Baseline Disease Characteristics

The following baseline disease characteristics will be summarized:

- Third agent in a subject's pre-existing treatment regimen
- HIV-1 RNA categories (copies/mL): (a) < 50, (b) ≥ 50
- CD4+ cell count (/μL)
- CD4+ cell count categories (/μL): (a) < 50, (b) ≥ 50 to < 200, (c) ≥ 200 to < 350, (d) ≥ 350 to < 500, and (e) ≥ 500
- CD4 percentage (%)
- Mode of infection (HIV risk factor)
- HIV disease status
- eGFR calculated using the Schwartz Formula
- Years diagnosed with HIV (to be calculated as time prior to first dose date)
- HBV surface antigen
- HCV antibody

6. EFFICACY ANALYSES

6.1. Definition of the Efficacy Endpoints

6.1.1. Efficacy Endpoints

The efficacy endpoints include:

- The percentage of subjects with plasma 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 counts and percentages at Weeks 24 and 48

The analyses for the efficacy endpoints will be conducted using the FAS

6.1.2. US FDA-Defined Snapshot Algorithm

The analysis window at Week 24 is defined as from Study Day 127 to Study Day 210, inclusive. The analysis window at Week 48 is defined as from Study Day 295 to Study Day 378, inclusive. The All HIV-1 RNA data collected on-treatment (ie, data collected up to 1 day after the last dose date of study drug) will be used in the US FDA-defined snapshot algorithm. Virologic outcome at Week 24 will be defined as the following categories:

HIV-1 RNA < 50 copies/mL: this includes subjects who have the last available on-treatment HIV-1 RNA < 50 copies/mL in the Week 24 analysis window

HIV-1 RNA ≥ 50 copies/mL: this includes subjects

1) Who have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL in the Week 24 analysis window, or
2) Who do not have on-treatment HIV-1 RNA data in the Week 24 analysis window and
    a) Who discontinue study drug prior to or in the Week 24 analysis window due to lack of efficacy, or
    b) Who discontinue study drug prior to or in the Week 24 analysis window due to AE or death and have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL or
    c) Who discontinue study drug prior to or in the Week 24 analysis window due to reasons other than AE, death, or lack of efficacy and have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL

No Virologic Data (in the Week 24 analysis window): this includes subjects who do not have on-treatment HIV-1 RNA data in the Week 24 analysis window because of the following:

1) Discontinuation of study drug prior to or in the Week 24 analysis window due to AE or death and the last available on-treatment HIV-1 RNA < 50 copies/mL or

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

3) Missing data during the window but on study drug

Virologic outcome at week 48 will be defined similarly by using the Week 48 anlaysis window.

6.1.3. Analysis Methods for Efficacy Endpoints

For the virologic outcome at Weeks 24 and 48 as defined by the US FDA defined snapshot algorithm, respectively, the numbers and percentages of subjects with HIV 1 RNA < 50 copies/mL, HIV 1 RNA ≥ 50 copies/mL (including subcategories), and no virological data (including reasons) will be summarized. The 95% confidence interval for the percentage estimate will be constructed using the Exact method.

Baseline values and changes from baseline in CD4 cell count (cells/μL) and CD4% at each visit will be summarized descriptively (sample size, mean, SD, 95% CI, median, Q1, Q3, minimum, and maximum) using observed, on-treatment data (ie, data collected up to 1 day after permanent discontinuation of study drug or all available data for subjects who were still on study drug).

7. SAFETY ANALYSES

Safety data will be summarized for the subjects in the safety analysis set. All safety data collected up to 30 days after permanent discontinuation of study drug or all available data for subjects who were still on study drug will be summarized, unless specified otherwise.

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory AEs will be coded using the MedDRA Version 22.1. System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lowest-level term (LLT) will be provided in the AE dataset.

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe) or Grade 4 (life threatening) according to toxicity criteria specified in the protocol. The severity grade of events for which the investigator did not record severity will not be imputed and will be left as "missing" for data listings.

7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected "Related" on the AE eCRF to the question of "Related to Study Treatment." Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-subject data listings will show the relationship as missing.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if AEs met the definitions of SAE specified in the study protocol. Serious adverse events captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Global Patient Safety (GLPS) Department before data finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as 1 or both of the following:

- Any AEs with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of the study drug, or
- Any AEs leading to premature discontinuation of study drug.

7.1.5.2. Incomplete Dates

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dosing date of study drug, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment emergent. The event is considered treatment emergent if both of the following 2 criteria are met:

- The month and year (or year) of the AE onset is the same as or after the month and year (or year) of the first dosing date of study drug, and
- The month and year (or year) of the AE onset is the same as or before the month and year (or year) of the date corresponding to 30 days after the date of the last dose of study drug

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date on or after the first dosing date of study drug, will be considered to be treatment emergent. In addition, an AE with the onset date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dosing date of study drug will be considered treatment emergent.

7.1.6. Summaries of Adverse Events and Deaths

Treatment-emergent AEs will be summarized based on the Safety Analysis Set.

A brief, high-level summary of the number and percentage of subjects who experienced at least 1 TEAE in the categories described below will be provided by treatment group. All deaths observed in the study will also be included in this summary.

The number and percentage of subjects who experienced at least 1 TEAE will be provided and summarized by SOC and PT for the following categories:

- TEAEs
- TESAEs
- TEAEs with grade 3 or higher
- TE treatment-related AEs
- TEAEs leading to premature discontunaton of study drug
- Death

Multiple events will be counted only once per subject in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC (and HLT within each SOC if applicable), and then by PT in descending order of total frequency within each SOC.

TEAEs and TESAEs will also be summarized up to Week 24. The AEs with onset date after the Week 24 nominal visit date will not be included in the analysis.

In addition, a data listing for all AEs, indicating whether the event is treatment emergent or not, will be provided.

7.2. Renal Safety Analysis

The following formula will be used to calculate eGFR:

Schwartz Formula:

$$\text{eGFR } (\text{ml/min/1.73m}^2) = \text{k} \times \text{L/SCr},$$

where

k is the proportionality constant (0.55 for children ≥ 2 to <12 years old and adolescent girls ≥ 12 years old; and 0.70 for adolescent boys ≥ 12 years old);
L is height (cm);
SCr is serum creatinine (mg/dL).

Baseline, postbaseline, and change from baseline in serum creatinine and $eGFR_{Schwartz}$ will be summarized by visit using descriptive statistics.

7.3. Bone Safety Analyses

The BMD will be evaluated in 2 body sites: spine and total body less head. BMD standard Z-score will be computed based on the chronological age-matched population of the same sex and ethnicity. BMD height-age Z-score will be generated by substituting height-age for chronological age, where height-age will be determined as the age at which the child's height is the median on the stature-for-age Centers for Disease Control (CDC) Year 2000 growth chart published on the following CDC website:

http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/index.htm

If a subject's height was greater than the median height for a 20-year-old according to the growth chart, both height-age and height-age Z-score will not be calculated. The BMD Z-scores (standard Z-score and height-age Z-score) will be calculated for the 2 body sites (ie, spine and total body less head).

CCI [redacted]

Descriptive summaries for the BMD Z-scores (standard Z-score and height-age Z-score) and the change from baseline in Z-scores (standard Z-score and height-age Z-score) will be presented by visit for the spine and total body less head DXA Analysis Sets.

7.4. Palatability/Acceptability Assessment

Palatability and acceptability assessments will be summarized by visit and cohorts using frequency count and percentage.

8. PHARMACOKINETICS ANALYSIS

8.1. PK Endpoints

The primary PK endpoints include:

- The PK parameter AUC_{tau} for TAF

The secondary PK endpoints include:

- Additional PK parameters including AUC_{last}, C_{max}, T_{max}, C_{last}, T_{last}, C_{tau}, λ_z, apparent CL, apparent V_z, and $T_{½}$)

The PK analysis for Cohort 1 was done in 2017 and will not be repeated in this analysis. Only IPK concentrations and parameters from Cohort 2 will be included in this analysis.

8.2. Estimation of Pharmacokinetic Parameters

Pharmacokinetic parameters from the intensive PK sampling will be estimated using WinNonlin® software using standard noncompartmental method. The linear/log trapezoidal rule will be used in conjunction with the appropriate noncompartmental model with input values for dose level, time of dose, plasma concentration, and corresponding real time values, based on drug dosing times whenever possible.

All predose sample times before time zero will be converted to zero. Samples below the limit of quantitation of the bioanalytical assays that occur prior to the achievement of the first quantifiable concentration will be assigned a concentration value of zero to prevent overestimation of the initial AUC. Samples that are BLQ at all other time points will be treated as missing data. The nominal time point for a key event or dosing interval (tau) may be used to permit direct calculation of AUC over specific time intervals. The appropriateness of this approach will be assessed by the pharmacokineticist on a profile-by-profile basis.

Accurate estimation of several PK parameters, such as λ_z and $t_{1/2}$, are dependent on the accurate estimation of the terminal elimination phase of the drug. The appropriateness of calculating these parameters will be evaluated upon inspection of PK data on a profile-by-profile basis by the pharmacokineticist.

8.3. Analysis for PK Parameters

Plasma concentration will be listed for all subjects and summarized by nominal time point for subjects in each PK analysis set for Cohort 2 by groups (ie. Group 1 with F/TAF 200/25 mg and Group 2 with F/TAF 120/15 mg).

PK parameters estimated for each analyte will be listed for all subjects and summarized for subjects in each PK analysis set for cohort 2 by groups (ie. Group 1 with F/TAF 200/25 mg and Group 2 with F/TAF 120/15 mg).

The descriptive statistics (n, mean, SD, coefficient of variation [%CV], minimum, median, maximum, Q1, Q3, geometric mean, and its 95% CI) will be presented for plasma concentration and parameter data. For concentration values BLQ, the number of subjects with values of BLQ will be presented. For PK parameter data, the geometric mean, its 95% CI, and the mean and SD of the natural-log transformed values will be presented in addition to the summaries mentioned above.

8.3.1. Statistical Comparative Analysis

To determine whether the adult dose in adolescents achieves similar systemic exposure to that in adults, statistical comparisons will be performed to compare the PK data from the current study with adult data from HIV-1 infected, F/TAF-treated subjects in Study GS-US-311-1089. The comparisons will be conducted in subgroup of subjects by the dose of F/TAF received (ie. 200/25 mg vs 120/15 mg).

For TAF, a one-way analysis of variance (ANOVA) model will be fitted to the natural logarithmic transformed values of AUC_{tau} (as the primary endpoint) and C_{max} (as the secondary endpoint), respectively, with treatment group as a fixed effect. The treatment groups are defined as the test treatment (adolescents in this study) and reference treatment (adults from Study GS-US-311-1089).

The PK parameters $AUC_{tau,}$ C_{max}, and C_{tau} for TFV will be analyzed similarly.

The ANOVA model will be carried out using the PROC MIXED procedure in SAS. An example SAS code is provided below:

```
Proc Mixed;
   by analyte paramcd;
   class group subjid;
   model lnest = group;
   repeated  / group = group;
   lsmeans group / e  diff cl alpha = 0.1;
   estimate 'Test  versus Reference'  group  1  1 / cl alpha = 0.10;
Run;
```

The geometric least-squares means (LS-means) of each treatment group, mean ratio (test/reference) and corresponding 90% CI for each PK parameter of the analytes will be reported.

The LSMEANS statement computes LS-means for each treatment group on the natural log scale. These values will then be exponentiated to produce the geometric LS-means on the original linear scale.

The ESTIMATE statement will produce the point estimate and 90% CI on the natural-log scale for the difference between treatments. The test/reference exposure ratio and associated 90% CIs will be calculated by exponentiation of the natural-log scale point estimate and the associated 90% CI lower and upper limits.

For each analyte, 90% CIs for the ratio of the geometric LS (GLS) means of the test (adolescents in this study) and reference (adults from Study GS-US-311-1089) treatments will be calculated for AUC_{tau}, C_{min}(if applicable), and C_{max}, consistent with the two 1-sided tests each performed at an alpha level of 0.05 {U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) 2001, U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) 2003}. Equivalency in PK will be concluded if the 90% CI are within the equivalence boundaries of 70% to 143%.

9. REFERENCES

U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for Industry. Statistical Approaches to Establishing Bioequivalence. January, 2001.

U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for Industry. Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations (Revision 1). March, 2003.

10. SOFTWARE

SAS® Software Version 9.4. SAS Institute Inc., Cary, NC, USA.

11. SAP REVISION

Revision Date (DD MMM YYYY)	Section	Summary of Revision	Reason for Revision

12. APPENDICES

Appendix 1. Schedule of Assessments

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] 1	2	4	8	12	24	36	48	CCI	30 Day Follow-up[e]	ESDD[f]
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] or 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 protocol 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]

cc [redacted]