STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 1b, Open-label study to Evaluate the PK, Safety and Efficacy of B/F/TAF in HIV-1 infected, Virologically Suppressed, Pregnant Women in their Second and Third Trimesters
Study Phase:	1b
Name of Test Drug:	Bictegravir/Emtricitabine/Tenofivir Alafenamide (B/F/TAF; GS-9883/F/TAF)
Study Number:	GS-US-380-5310
Protocol Version (Date):	Original (02 April 2019)
Analysis Type:	Final Analysis
Analysis Plan Version:	Version 1.0
Analysis Plan Date:	15 Nov 2022
Analysis Plan Author(s):	PPD PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

TABLE OF CONTENTS

STATISTICAL ANALYSIS PLAN 1
TABLE OF CONTENTS 2
LIST OF ABBREVIATIONS 5
PHARMACOKINETIC ABBREVIATIONS 7
1. INTRODUCTION 8
1.1. Study Objectives 8
1.2. Study Endpoints 9
1.3. Study Design 9
1.4. Sample Size and Power 12
2. TYPE OF PLANNED ANALYSIS 13
2.1. Interim Analysis 13
2.1.1 Planned Interim Analysis 13
2.1.2 Data Monitoring Committee Analyses 13
2.2. Final Analysis 13
2.3. Changes from Protocol-Specified Analysis 13
3. GENERAL CONSIDERATIONS FOR DATA ANALYSES 14
3.1. Analysis Sets 14
3.1.1. All Enrolled Analysis Set 14
3.1.2. Analysis Sets Used for Adult Analysis 15
3.1.2.1. Safety Analysis Set 15
3.1.2.2. Full Analysis Set 15
3.1.2.3. Pharmacokinetics Analysis Set 15
CCI [redacted]
3.2. Strata and Covariates 15
3.3. Examination of Participant Subgroups 16
3.4. Multiple Comparisons 16
3.5. Missing Data and Outliers 16
3.5.1. Missing Data 16
3.5.2. Outliers 16
3.6. Data Handling Conventions and Transformations 16
3.7. Analysis Visit Windows and Visit Definitions 18
3.7.1. Definition of Study Day 18
3.7.1.1. Definition of Study Day for Adults 18
CCI [redacted]
3.7.2. Analysis Visit Windows and Analysis Visits 19
3.7.2.1. Analysis Windows for Adults 19
CCI [redacted]
3.7.3. Selection of Data in the Event of Multiple Records in an Analysis Visit Window 22
4. SUBJECT DISPOSITION 24
4.1. Enrollment and Disposition 24
4.2. Extent of Study Drug Exposure and Adherence 25
4.2.1. Duration of Exposure to Study Drug 25

4.2.2. Adherence to Study Drug Regimen 25
4.3. Protocol Deviations 26
4.4. Assessment of COVID-19 Impact 27
4.4.1. Study Drug or Study Discontinuation Due to COVID-19 27
4.4.2. Protocol Deviations Due to COVID-19 27
4.4.3. Missed and Virtual Visits Due to COVID-19 27
4.4.4. Adverse Events Due to COVID-19 27
5. BASELINE CHARACTERISTICS 28
5.1. Demographics and Baseline Characteristics 28
5.2. Other Baseline Characteristics 28
5.3. Medical History 29
6. EFFICACY ANALYSES 30
6.1. Efficacy Endpoints 30
6.2. Analysis of the Efficacy Endpoints 30
6.2.1. Analysis of CD4+ Cell Count 31
6.2.2. Analysis of CD4% 31
6.3. Changes From Protocol-Specified Efficacy Analyses 31
7. SAFETY ANALYSES 32
7.1. Adverse Events and Deaths 32
7.1.1. Adverse Event Dictionary 32
7.1.2. Adverse Event Severity 32
7.1.3. Relationship of Adverse Events to Study Drug 32
7.1.4. Relationship of Adverse Events to Study Procedure 32
7.1.5. Serious Adverse Events 32
7.1.6. Treatment-Emergent Adverse Events 33
7.1.6.1. Definition of Treatment Emergent Adverse Events 33
7.1.6.2. Incomplete Dates 33
7.1.7. Summaries of Adverse Events and Deaths 33
7.1.7.1. Treatment-emergent Adverse Events for adult participants 34
7.1.7.2. Adverse Events for neonate participants 35
7.1.8. Additional Analysis of Adverse Events 36
7.1.8.1. A Stage 3 Opportunistic Illnesses in HIV 36
7.2. Laboratory Evaluations 36
7.2.1. Summaries of Numeric Laboratory Results 37
7.2.2. Graded Laboratory Values 37
7.2.2.1. Treatment-Emergent Laboratory Abnormalities 38
7.2.2.2. Summaries of Laboratory Abnormalities 38
7.2.3. Liver-Related Laboratory Evaluations 39
7.2.4. Renal-Related Laboratory Evaluations 39
7.2.4.1. Serum Creatinine and $eGFR_{CG}$ 39
7.3. Body Weight, Height, BMI, and Vital Signs 40
7.4. Prior and Concomitant Medications 40
7.4.1. Nonstudy Drug Antiretroviral Medications 40
7.4.2. Concomitant Non-ARV Medications 40
7.5. Electrocardiogram Results 41
7.6. Other Safety Measures 41
7.7. Changes From Protocol-Specified Safety Analyses 41
8. PHARMACOKINETIC EVALUATION/ANALYSIS 42
8.1. Estimation of Pharmacokinetic Parameters 42
8.2. Pharmacokinetic Parameters 42

8.3. Statistical Analysis Methods 43
8.3.1. General Considerations 43
8.3.2. Statistical Methodology 45
8.4. Sensitivity Analysis 47
9. REFERENCES 48
10. SOFTWARE 49
11. SAP REVISION 50
APPENDICES 51
Appendix 1. Maternal and Neonatal Study Procedures Tables 51
Appendix 2. Adverse Events of COVID-19 and Suspected COVID-19 Infection 54
Appendix 3. Data Collection of COVID-19 Data 55
Appendix 4. Programming Specification 56

LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AQL	above quantitation limit
ARV	Antiretroviral
AST	aspartate aminotransferase
BE	bioequivalence
B/F/TAF	bictegravir/emtricitabine/ tenofovir alafenamide, Biktarvy®
BIC	bictegravir, B, GS-9883
BLQ	below the limit of quantitation
BMI	body mass index
CFR	Code of Federal Regulations
CI	confidence interval
CRF	case report form
CSR	clinical study report
CTCAE	Common Toxicity Criteria for Adverse Events
DMC	data monitoring committee
ECG	electrocardiogram
ET	early termination
EVG	elvitegravir, E
FAS	Full analysis set
FDC	fixed dose combination
FTC	emtricitabine
Gilead	Gilead Sciences
GLSM	geometric least-squares mean
Hb	hemoglobin
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetic
PP	per protocol
PT	preferred term
Q1, Q3	first quartile, third quartile
SAP	statistical analysis plan
SD	standard deviation
SI	International System of Units (Systeme International d'Unites)
SOC	system organ class
TAF	tenofovir alafenamide
TEAE	treatment-emergent adverse event

TFLs	tables, figures, and listings
TFV-DP	tenofovir diphosphate
ULOQ	upper limit of quantification
ULN	upper limit of normal
VR	ventricular rate
WHO	World Health Organization

PHARMACOKINETIC ABBREVIATIONS

λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the log plasma/serum concentration of drug versus time curve of the drug
AUC	area under the plasma/serum concentration versus time curve
$\%AUC_{exp}$	Percentage of AUC extrapolated between AUC_{last} and AUC_{inf}
AUC_{inf}	area under the plasma/serum concentration versus time curve from time zero to infinity
AUC_{last}	area under the plasma/serum concentration versus time curve from time zero to the last quantifiable concentration
AUC_{tau}	area under the plasma/serum concentration versus time curve from time zero to tau (dosing interval)
CL_{ss}/F	apparent clearance after administration of the drug at steady state: $CL_{ss}/F = Dose/AUC_{0\text{-}tau}$, where "Dose" is the dose of the drug
C_{last}	last observed quantifiable plasma/serum concentration of the drug
C_{max}	maximum observed plasma/serum concentration of drug
$t_{½}$	estimate of the apparent terminal half-life of the drug in plasma/serum, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
T_{last}	time (observed time point) of C_{last}
T_{max}	time (observed time point) of C_{max}
V_z/F	Apparent volume of distribution of the drug

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-380-5310. This SAP is based on the study protocol dated 02 April 2019 and the electronic case report form (eCRF). The SAP will be finalized prior to database finalization. Any changes made after 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 steady state pharmacokinetics (PK) of bictegravir (BIC) and confirm the dose of BIC/emtricitabine/tenofovir alafenamide (B/F/TAF) 50/200/25 mg fixed dose combination (FDC) in the second and third trimesters of pregnancy

The secondary objectives of this study are as follows:

- To evaluate the steady state PK of emtricitabine (FTC) and TAF in the second and third trimesters of pregnancy
- To evaluate maintenance of HIV-1 virologic suppression in pregnant women receiving the B/F/TAF FDC during the second and/or third trimesters

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1.2. Study Endpoints

The primary endpoint of this study is:

- The PK parameter AUC_{tau} of BIC during the second and/or third trimesters through post-partum

The secondary endpoints of this study are:

- The PK parameter AUC_{tau} for FTC and TAF, and PK parameters AUC_{last}, C_{max}, C_{tau}, C_{last}, T_{max}, $T_{1/2}$, CL/F, V_z/F, and λ_z for BIC, FTC, and TAF, as applicable
- The proportion of participants with plasma HIV-1 RNA < 50 copies/mL at the time of delivery by missing = excluded approach

1.3. Study Design

This is an open-label, multicenter, multiple-dose study to evaluate the PK, efficacy, safety and tolerability of B/F/TAF in virologically suppressed, HIV-1 infected pregnant women in their second and third trimesters.

At least 25 participants will be enrolled to obtain at least 20 evaluable pairs of PK assessments between the second trimester and post-partum and at least 20 evaluable pairs of PK assessments between the third trimester and post-partum. Replacement participants may be enrolled if originally enrolled participants do not complete all intensive PK visits as expected.

Infants born to women participating in the study will be followed from birth to 4-8 weeks of age if consent is obtained from the parents/legal guardian.

Participants will be treated with B/F/TAF for up to approximately 38 weeks (from the second or third trimesters of pregnancy, depending on enrollment, through 12 weeks post-partum). Participants who complete the study through the Week 12 post-partum visit will be required to return to the clinic 30 days after the Week 12 post-partum visit for a 30-Day Follow-Up Visit.

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Following completion of Screening and Day 1 visits, eligible participants will be required to return for study visits at Weeks 4, 8, 12, 16, 20 and 24 dependent on time of enrollment (unless delivery has occurred by that time point). The day of delivery will be considered as the Delivery Visit for study purposes.

Following delivery, participants will be required to return for study visits for Weeks 6 and 12 post-partum visits and a 30-Day Follow-up Visit.

For all eligible participants, blood samples will be collected at Day 1 and all subsequent visits.

For all eligible participants, urine samples will be collected at Day 1, Weeks 12 and 24, and Weeks 6 and 12 post-partum visits.

Pharmacokinetic Assessments

- **Study Drug Administration for Intensive Pharmacokinetic:** On the days of intensive pharmacokinetic (iPK) sampling, study drug will be administered in the morning in the clinic. Following study drug administration participants will fast until after collection of the 2 hour PK sample. If a subject is unable to fast for the iPK visit, the visit may proceed. Participants should be consistent if they choose to fast or not fast during the iPK visits (i.e. if the participant fasts at the first iPK visit, then they should fast at all other iPK visits).
- **PK Collection During Preganancy:** Intensive PK (iPK) visits will be completed after participant administers B/F/TAF for at least 3 weeks.

  For participants who enroll during the second trimester, serial blood samples for iPK evaluation will be collected at or between 20 to 28 weeks of gestation, and during the third trimester, at or between 30 to 38 weeks of gestation.

  For participants who enroll during the third trimester, serial blood samples for iPK evaluation will be collected at or between 30 to 38 weeks of gestation.
- **PK Collection Post-partum:** Serial blood samples for iPK evaluation will be collected for all participants at Week 6 and Week 12 post-partum visits.
- **Intensive PK Sample Collection Timepoints:** Blood samples will be collected at the following time points at the iPK visits:

  — Pre-dose (≤ 5 minutes prior to dosing)

  — 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours post-dose

  A single anytime PK sample will be collected at the Early Study Drug Discontinuation (ESDD) Visit, if applicable.

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- **Sparse PK Collection at the Delivery Visit:** A single maternal blood sample and an umbilical cord blood sample after cord clamping will be collected soon after delivery.

Safety Assessments

- Complete physical exam: Screening, Day 1, Week 4, Week 12, Weeks 6 and 12 post-partum, and at the ESDD Visit, if applicable
- Symptom-driven physical exam: Weeks 8, 16, 20 and 24, and 30-Day Follow-up Visit
- Vital signs (blood pressure, heart rate, respiration rate, and body temperature): Screening, Day 1 and all subsequent visits
- Height: Screening

- Weight: Screening, Day 1 and all subsequent visits
- Estimated glomerular filtration (eGFR) rate according to the Cockcroft-Gault formula: Screening, Day 1, Weeks 12 and 24, and Weeks 6 and 12 post-partum visits
- Clinical laboratory tests (hematology, chemistry, and urinalysis): Screening, Day 1, Weeks 12 and 24, Weeks 6 and 12 post-partum, 30-Day Follow-up Visit and at the ESDD visit, if applicable
- Maternal alfa-fetoprotein level: Screening
- Urine drug and alcohol assessments: Screening, Day 1
- 12-lead electrocardiogram (ECG): Screening
- Hepatitis B virus, hepatitis C virus testing: Screening
- HIV-1 RNA testing: Screening, Day 1 and all subsequent visits
- CD4+ cell count: Screening, Day 1, and Week 12 post-partum visit

Assessments at the Delivery Visit

- At the Delivery Visit, the date of delivery and outcome of the pregnancy will be recorded and a blood sample will be collected for HIV-1 RNA testing. Additionally, blood samples will be collected for PK assessments as described above.
- Assessment of adverse events (AEs) and concomitant medications will continue throughout the study. All clinical and clinically significant laboratory toxicities will be managed per protocol requirements.

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Sparse PK Collection

Sparse PK blood samples will be collected, if possible, at the following time points: at or between 0 to < 2 hours, 2 to < 3 hours, 3 to 8 hours, 18 to 28 hours, 36 to 72 hours, and 5 to 7 days after birth.

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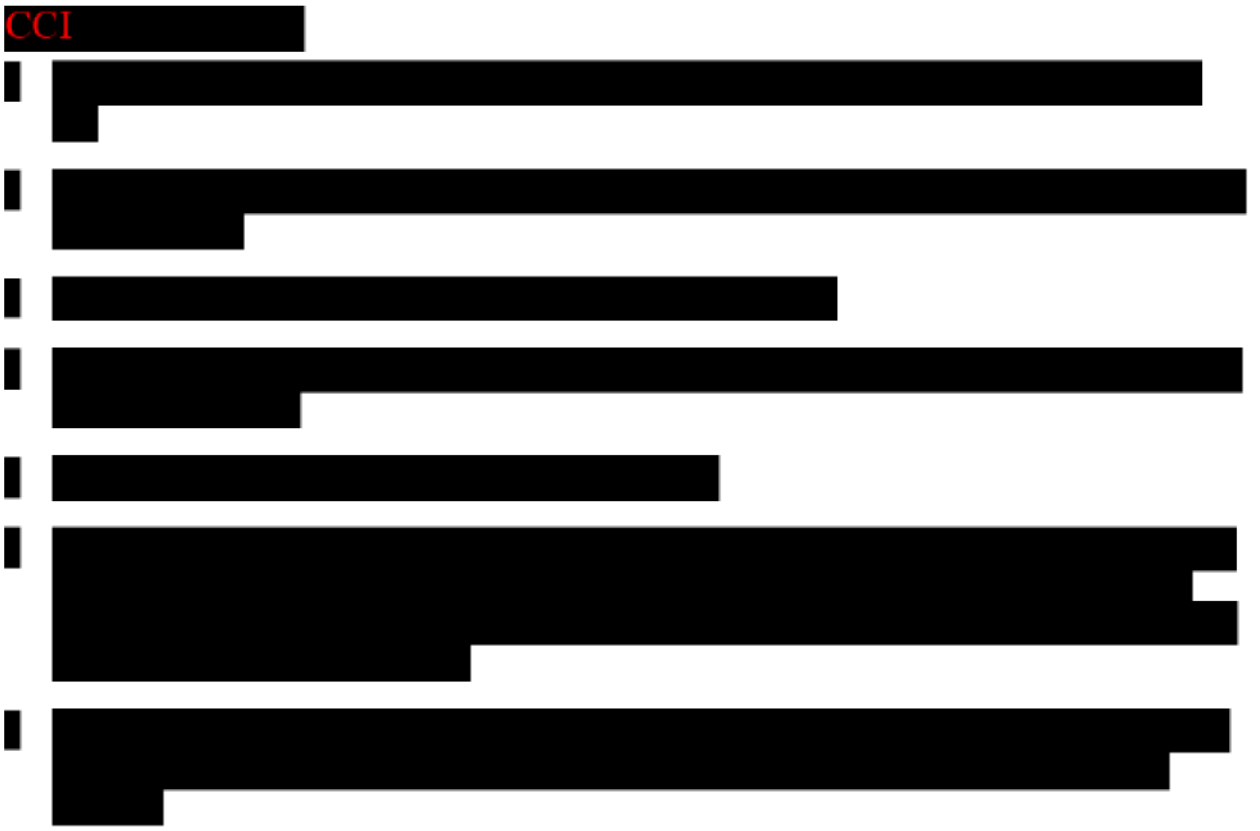

1.4. Sample Size and Power

With 20 evaluable participants, the study has at least 74% power to show that the lower bound of the 90% CI of the ratio for AUC_{tau} of BIC during pregnancy relative to post-partum is > 50%, assuming a decrease of 40% in AUC_{tau} of BIC during pregnancy relative to post-partum. It was assumed that a standard deviation (SD) of BIC AUC_{tau} is no more than 0.34 on a natural logarithm scale, which is supported by a pooled PK analysis from 4 previous Gilead Phase 3 studies. With 25% overage, a total sample size of at least 25 participants will be required. Sample size and power calculations were made using the statistical software package nQuery Advisor (Version 8.5.1).

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analysis

2.1.1 Planned Interim Analysis

No interim analysis is planned.

2.1.2 Data Monitoring Committee Analyses

This study does not have a data monitoring committee (DMC). Therefore, no analyses will be conducted for the DMC.

2.2. Final Analysis

After all participants have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized, the final analysis of the data will be performed. The analysis of the primary endpoint will be conducted at the time of the final analysis.

2.3. Changes from Protocol-Specified Analysis

No changes from protocol-specified analyses are planned.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of participants in each category will be presented; for continuous variables, the number of participants (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 participants in the All Enrolled Analysis Set, and sorted by participant identification (ID) number in ascending order, visit date, and time (if applicable), unless otherwise specified. Data collected on log forms, such as AEs, will be presented in chronological order within participant. Age, sex at birth, race, and ethnicity will be included in the listings, as space permits.

In general, for adult participants, age (in years) on the date of the first dose of study drug will be used for analyses and presentation in listings. 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. Age is set as 1 day for Neonate participants at enrollment.

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 participants to be included in an analysis. Analysis sets and their definitions are provided in this section. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

For each analysis set, the number and percentage of participants eligible for inclusion will be summarized. A listing of reasons for exclusion from analysis sets will be provided by participant.

3.1.1. All Enrolled Analysis Set

The All Enrolled Analysis Set includes all participants who enrolled into the study. This includes adult participants and infants born to women participating in the study.

3.1.2. Analysis Sets Used for Adult Analysis

3.1.2.1. Safety Analysis Set

The Safety Analysis Set includes all adult participants who took at least 1 dose of study drug (i.e., B/F/TAF). This is the primary analysis set for adult safety analyses.

3.1.2.2. Full Analysis Set

The Full Analysis Set includes all adult participants who enrolled into the study and took at least 1 dose of study drug (i.e., B/F/TAF). This is the primary analysis set for adult efficacy analyses.

3.1.2.3. Pharmacokinetics Analysis Set

The PK (Pharmacokinetics) Analysis Sets include all enrolled adult participants who took at least 1 dose of study drug (i.e., B/F/TAF), and have at least 1 nonmissing concentration value reported by the PK laboratory for the corresponding analytes (i.e., BIC, FTC, TAF, and TFV-DP). These are the primary analysis sets for all adult PK analyses.

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3.2. Strata and Covariates

This study does not use a stratified randomization schedule in enrolling participants.
No covariates will be included in the analyses.

3.3. Examination of Participant Subgroups

There are no prespecified participant subgroupings for analyses.

3.4. Multiple Comparisons

Adjustments for multiplicity will not be made for testing, because no formal statistical testing will be performed in this study.

3.5. Missing Data and Outliers

3.5.1. 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 participant 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.

The handling of missing or incomplete dates for AE onset is described in Section 7.1.6.2, and for concomitant medications in Section 7.4.2.

3.5.2. Outliers

Outliers will be identified during the data management and data analysis process, but no sensitivity analyses will be done, unless specified otherwise. All data will be included in the analyses.

3.6. Data Handling Conventions and Transformations

The following conventions will be used for the imputation of date of birth when it is partially missing or not collected:

- If only month and year of birth is collected, then "15" will be imputed as the day of birth
- If only year of birth is collected, then "01 July" will be imputed as the day and month of birth
- If year of birth is missing, then date of birth will not be imputed. In general, age collected at Day 1 (in years) will be used for analyses and presented in listings.

In general, age collected at Day 1 (in years) will be used for analyses and presented in listings. If age at Day 1 is not available for a participant, then age derived based on date of birth and the Day 1 visit date will be used instead.

Non-PK Data that are continuous in nature but are less than the lower limit of quantitation (LLOQ) or above the upper limit of quantification (ULOQ) will be imputed as follows:

- A value that is 1 unit less than the LLOQ will be used to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the LLOQ). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used to calculate 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 to calculate summary statistics.

- A value that is 1 unit above the ULOQ will be used to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the ULOQ). Values with decimal points will follow the same logic as the bullet point above.

- The limit of quantitations will be used to calculate descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the limit of quantitations, i.e., LLOQ and ULOQ).

If methods based on the assumption that the data are normally distributed are not adequate, analyses may be performed on transformed data or nonparametric analysis methods may be used, as appropriate.

Natural logarithmic transformation will be used for plasma concentrations and analysis of PK parameters. Plasma concentration values that are below the limit of quantitation (BLQ) will be presented as "BLQ" in the concentration data listing. For adult participants, values that are "BLQ" will be treated as 0 at predose time points, and one-half the value of LLOQ at postdose time points for determination of summary and order statistics. For neonate participants, values that are BLQ will be treated as one-half the value of the LLOQ for determination of summary and order statistics. PK concentration result of "AQL" (i.e., above quantitation limit) will be imputed as the ULOQ + 1 for adults and CCI to compute the summary and order statistics. For maternal and umbilical cord plasma PK concentrations, values of "BLQ" and "AQL" will be imputed using the same rule to calculate the summary and order statistics on those analytes, but the cord blood to maternal plasma concentration ratio will not be imputed if any value of cord blood or maternal plasma concentration is "BLQ" or "AQL".

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

- If at least 1 participant 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) and summary statistics will be displayed as "BLQ".

PK parameters that are "BLQ" will be imputed as one-half LLOQ before log transformation or statistical model fitting.

For urine creatinine, a value of "< 1" is handled as a missing value in its summary and the calculation of related ratios.

Logarithmic (base 10) transformations will be applied to HIV-1 RNA for efficacy analyses. 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.

3.7. Analysis Visit Windows and Visit Definitions

3.7.1. Definition of Study Day

3.7.1.1. Definition of Study Day for Adults

Study Day 1 is defined as the day when the first dose of the study drug (i.e., B/F/TAF) was taken for adults, as recorded on the Study Drug Administration eCRF.

Baseline value is defined as the last value obtained on or prior to Study Day 1 for all assessments except pharmacokinetic analysis.

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 defined as the latest study drug end dates recorded on the Study Durg Administration eCRF with "Permanently Withdrawn" box checked for participants who prematurely discontinued or completed study drug according to the Study Drug Completion eCRF.

Predose value for PK analysis, is defined as the last available off-treatment value collected prior to the first dose of study drug.

Postdose value for PK analysis, is defined as any value collected after the first dose of study drug until the last PK sample collection at the Week 12 post-partum visit.

Value at Delivery is defined as the last value obtained on the date of delivery for all assessments.

Post-partum Study Days are calculated relative to date of delivery. For events that occurred on or after the date of delivery, study days are calculated as (visit date minus date of delivery plus 1).

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3.7.2. Analysis Visit Windows and Analysis Visits

Participant visits might not occur on protocol specified days. Therefore, for the purpose of analysis, observations will be assigned to two different analysis windows: the analysis windows for the adult analysis are derived relative to the date of first dose of the study drug (i.e., B/F/TAF) before delivery, and the date of delivery for post-partum, respectively. No analysis windows are applied for neonate participants.

3.7.2.1. Analysis Windows for Adults

The analysis windows for HIV-1 RNA, CD4+ cell count, vital signs (including weight), are presented in to Table 3-1**Error! Reference source not found.** to Table 3-3. Post-partum windows refer to delivery for nominal visit and lower/upper limits calculation.

Table 3-1. Pre-partum Analysis Windows for HIV-1 RNA and Vital Signs

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 4	28	2	42
Week 8	56	43	70
Week 12	84	71	98
Week 16	112	99	126
Week 20	140	127	154
Week 24	168	155	182
Week K (K is every 4 weeks after previous visit before delivery dependent on time of enrollment)	K*7	(K-2)*7+1	Min((K+2)*7,delivery day)

Baseline value is defined as the last value obtained on or prior to Study Day 1 for all assessments. The pre-partum analysis window's definition is based on Study Days.

Table 3-2. Post-partum Analysis Windows for HIV-1 RNA and Vital Signs

Visit ID	Nominal Day	Lower Limit	Upper Limit
Delivery			1
Week 6 post-partum	42	2	63
Week 12 post-partum	84	64	105
Week K post-partum (K is every 6 weeks)	K*7	(K-3)*7+1	(K+3)*7

Value at Delivery is defined as the value obtained on or the date of delivery for all assessments. The post-partum analysis window's definition is based on post-partum Study Days.
Vital Signs were not measured at the date of delivery.

Table 3-3. Post-partum Analysis Windows for CD4+ cell count and CD4 %

Visit ID	Nominal Day	Lower Limit	Upper Limit
Delivery			1
Week 12 post-partum	84	2	105
Week K post-partum (K is every 6 weeks)	K*7	(K-3)*7+1	(K+3)*7

The post-partum analysis window's definition is based on the day of delivery.
CD4 cell counts and percentage were not measured at the date of delivery.

The analysis windows for hematology, chemistry, urinalysis, urine pregnancy laboratory tests (collected after delivery only), $eGFR_{CG}$, are presented in Table 3-4 and Table 3-5.

Table 3-4. Pre-partum Analysis Windows for Hematology, Chemistry, Urinalysis, Urine Pregnancy Laboratory Tests, and $eGFR_{CG}$

Visit ID	Nominal Day	Lower Limit	Upper Limit
Baseline			1
Week 12	84	2	126
Week 24	168	127	210
Week K (K is every 12 weeks after previous visit before delivery dependent on time of enrollment)	K*7	(K-6)*7+1	Min((K+6)*7,delivery day)

Baseline value is defined as the last value obtained on or prior to Study Day 1 for all assessments. The pre-partum analysis window's definition is based on Study Days.

Table 3-5. Post-partum Analysis Windows for Hematology, Chemistry, Urinalysis, Urine Pregnancy Laboratory Tests, and $eGFR_{CG}$

Visit ID	Nominal Day	Lower Limit	Upper Limit
Delivery			1
Week 6 post-partum	42	2	63
Week 12 post-partum	84	64	105
Week K post-partum (K is every 6 weeks)	K*7	(K-3)*7+1	(K+3)*7

The post-partum analysis window's definition is based on the day of delivery.
No laboratory data were measured at the date of delivery.

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

This section only applies to adult participants analysis, and not applicable to neonate participants analysis.

Depending on the statistical analysis method, single values may be 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 1 value per analysis window.

If multiple valid, nonmissing numeric obserfvations exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- For baseline, the last nonmissing value on or prior to the first dosing date of study drug will be selected, unless specified differently. If there are multiple records with the same time or no time recorded on the same day, the baseline value will be the average of the measurements for continuous data, except for HIV-1 RNA (see below), or the measurement with the lowest severity (eg, normal will be selected over abnormal for safety electrocardiogram [ECG] findings) for categorical data.

- For postbaseline values:

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

  — For other numeric observations (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 observations except HIV-1 RNA, if there are multiple records on the selected day, the average will be taken for continuous data and the worse severity will be taken for categorical data, unless otherwise specified.

- For baseline and postbaseline HIV-1 RNA, the latest (considering both collection date and time) record(s) in the window will be selected. If both "HIV RNA Taqman 2.0" and "HIV RNA Repeat" (i.e., 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 safety ECG findings).

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

4. SUBJECT DISPOSITION

4.1. Enrollment and Disposition

4.1.1 Enrollment

Key study dates (i.e., first participant screened, first participant enrolled, last participant enrolled, last participant last visit for the primary endpoint, and last participant last visit for the clinical study report) will be provided.

A summary of participant enrollment will be provided by adults, CCI and total participants for each country and investigator.

4.1.2. Disposition

Summaries of participant disposition will be provided for adult and neonate participants, respectively.

These summaries will present the number of participants in each of the categories listed below:

- Participants screened (for Adults CCI)
- Screen failure participants who were not enrolled (for Adults CCI)
- Participants met all eligibility criteria and not enrolled (for Adults CCI)
- Participants enrolled (for Adults CCI)
- Participants enrolled and never treated (for Adults only)
- Participants in Safety Analysis Set (for Adults CCI)
- Participants in Full Analysis Set (for Adults CCI)
- Participants who completed study drug (for Adults only)
- Participants who prematurely discontinued study drug with reasons (for Adults only)
- Participants who completed study (for Adults only)
- Participants who prematurely discontinued from study with reasons (for Adults only)

For the status of study drug and study completion and reasons for premature discontinuation, the number and percentage of participants in each category will be provided for Adult participants only. The denominator for the percentage calculation will be the total number of participants in the Safety Analysis Set. In addition, a flowchart will be provided to depict the disposition.

A by-subject listing of participant disposition including date of the dose of study drug (study day) (CCI), study drug completion status (CCI), reason for study drug discontinuation CCI , study completion status CCI , reason for study discontinuation CCI , and PK set status (indicating whether or not a participant is included in the PK analysis set) will be provided by participant ID number in ascending order.

4.2. Extent of Study Drug Exposure and Adherence

Study Drug exposure and adherence only applies to adult participants analysis.

4.2.1. Duration of Exposure to Study Drug

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).

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 participants 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 participants in the Safety Analysis Set for adult participants. No inferential statistics will be provided.

4.2.2. Adherence to Study Drug Regimen

Study drug regimen adherence will be computed based on pill counts. The numbers of pills of study drug dispensed and returned are captured on study drug accountability eCRF.

Adherence (%) of study drug regimen will be calculated as follows:

$$\text{Adherence}(\%) = 100 \times \frac{\text{Total No. of pills taken}}{\text{Total No. of pills prescribed}}$$

$$= 100 \times \frac{\sum \text{No. of pills taken at each dispensing period}^{[1]}}{\sum \text{No. of pills prescribed at each dispensing period}^{[2]}}$$

[1] Number of pills taken at a distinct dispensing period for a study drug is calculated as the minimum of (a) the daily number of pills prescribed for the study drug multiplied by the duration of treatment at the dispensing period, and (b) the number of pills taken for the study drug (number of pills dispensed minus the number of pills returned). Total number of pills taken is determined by summing the number of pills taken from all evaluable dispensing periods.

[2] Number of pills prescribed at a distinct dispensing period for a study drug is calculated as the daily number of pills prescribed for the study drug multiplied by the duration of treatment at the dispensing period. Total number of pills prescribed is determined by summing the number of pills prescribed from all evaluable dispensing periods.

The duration of treatment at a dispensing period for a study drug is calculated as the minimum of (a) the last returned date of study drug at a dispensing period, (b) date of premature

discontinuation of the study drug, and (c) next pill dispensing date of the study drug, minus dispensing date of the study drug.

The next pill dispensing date is the following dispensing date of the study drug regardless of the bottle return date.

For a record where the number of pills returned was missing (with "Yes" answered for "Was Bottle returned?" question), it is assumed the number of pills returned was zero. If the number of pills dispensed was missing or any study drug bottle was not returned or the bottle return status was unknown, then all records in that dispensing period for that study drug will be excluded from both denominator and numerator calculation.

Adherence will be calculated using all data from the entire dosing period up to the date of permanent discontinuation of the study drug for participants who prematurely discontinued study drug or completed study drug.

Descriptive statistics for adherence for a study drug regimen (n, mean, SD, median, Q1, Q3, minimum, and maximum) along with the number and percentage of participants belonging to adherence categories (eg, $< 80\%$, $\geq 80\%$ to $< 90\%$, $\geq 90\%$ to $< 95\%$, $\geq 95\%$) will be provided for participants who return at least 1 bottle and have calculable adherence during the study in the Safety Analysis Set for adult participants. No inferential statistics will be provided.

A by-subject listing will be provided to display study drug administration data, including planned timepoint, study drug, dose date and time, dose and unit of study drug. This only applies to adult participants. A by-subject listing of study drug accountability will be provided separately by participant ID number (in ascending order) and visit (in chronological order) for adult participants.

4.3. Protocol Deviations

A by-subject listing will be provided for those participants who violated at least 1 eligibility (inclusion or exclusion) criterion but got enrolled in the study. The listing will present the entry criterion (or criteria if more than 1 violation) that participants did not meet and related comments, if collected.

Protocol deviations occurring after participants entered the study are documented during routine monitoring. The number and percentage of participants with important protocol deviations by deviation category (eg, eligibility criteria, informed consent) will be summarized based on the number of adult and neonate participants in the All Enrolled Analysis Set, respectively.

Any important deviations identified will be included in a by-subject listing, and evaluated to determine if it justifies excluding the participant from any analysis sets. If no IPD exists, an empty listing will be created.

4.4. Assessment of COVID-19 Impact

This study was ongoing during the novel coronavirus (COVID-19) pandemic which has an impact on the study conduct. Some participants were unable to attend onsite visits due to shelter in place guidelines, site closures, or other reasons. This section describes how special situations due to COVID-19 will be handled in the analysis.

4.4.1. Study Drug or Study Discontinuation Due to COVID-19

A by-subject listing of reasons for premature study drug or study discontinuation due to COVID-19 will be provided if applicable. This only applies to adult participants.

4.4.2. Protocol Deviations Due to COVID-19

A by-subject listing will be provided for participants with important protocol deviations related to COVID-19 if applicable. A separate listing will be provided for participants with non-important protocol deviations related to COVID-19 if applicable.

4.4.3. Missed and Virtual Visits Due to COVID-19

A by-subject listing of participants with missed or virtual visits due to COVID-19 will be provided by participant ID number in ascending order.

Information regarding missed or virtual visits due to COVID-19 will be collected as free text in the CRF comment fields. The determination of missed or virtual visits due to COVID-19 will be done using Natural Language Processing (NLP) to search the CRF comment fields. A detailed explanation of the algorithm is given in Appendix 2.Adverse Events of COVID-19 and Suspected COVID-19 Infection.

4.4.4. Adverse Events Due to COVID-19

AEs of COVID-19 will be included in analyses of AEs if applicable, which will be determined through COVID-19 **SMQ Narrow** search. A by-subject listing of AEs of COVID-19 will be provided if applicable.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Participant demographic variables (i.e., age, sex, race, and ethnicity) and baseline characteristics (body weight [in kg], height [in cm], body mass index [BMI; in kg/m^2; for adult participants only]) will be summarized overall using descriptive statistics for continuous variables and using number and percentage of participants for categorical variables. The summary of demographic and baseline data will be provided for the Safety Analysis Set and Neonate Safety Analysis Set, respectively.

A by-subject demographic listing, including the informed consent date, will be provided by participant ID number in ascending order.

5.2. Other Baseline Characteristics

The following other baseline characteristics (or baseline disease characteristics) will also be included and summarized using descriptive statistics for the Safety Analysis Set and Neonate Safety Analysis Set, respectively.

For adult participants analysis:

- 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 factors)
- HIV disease status
- $eGFR_{CG}$ (mL/min)
- ECG (Normal/Abnormal)

For neonate participants analysis:

- HIV-1 RNA categories (copies/mL): (a) < 50, (b) ≥ 50
- Apgar score

- Head circumference (cm)
- Anthropometric measures

Apgar score and Anthropometric measures will be summarized as numeric variables in baseline disease characteristcs.

A by-subject listing of other baseline characteristics will be provided by participant ID number in ascending order.

5.3. Medical History

General medical history data will be collected at screening for adult participants only. General medical history data will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA).

A summary of disease-specific medical history will be provided for the Safety Analysis Set for adult participants. No formal statistical testing is planned.

A by-subject listing of medical history will be provided for all adult participants by participant ID number in ascending order.

6. EFFICACY ANALYSES

The analyses for the efficacy endpoints will be conducted using the Full Analysis Set and Neonate Full Analysis Set, respectively. Analysis for CD4+ cell count endpoint only applies to analysis on adult participants. CCI [redacted]

6.1. Efficacy Endpoints

The efficacy endpoints include the following:

- The proportion of maternal participants with plasma HIV-1 RNA < 50 copies/mL at the time of delivery
- The change from baseline in CD4+ cell count at Week 12 post-partum visit
- The change from baseline in CD4% at Week 12 post-partum visit

6.2. Analysis of the Efficacy Endpoints

6.2.1 Analysis of the proportion of participants with plasma HIV-1 RNA < 50 copies/mL by missing = excluded (M = E) approach

The proportion of participants with HIV-1 RNA < 50 copies/mL will be analyzed using the M = E method. In this approach, all missing data will be excluded in the computation of the percentages (i.e., missing data points will be excluded from both the numerator and denominator in the computation). The denominator for percentages at a visit is the number of participants in the FAS with nonmissing HIV-1 RNA value at that visit.

The number and percentage of participants with HIV-1 RNA in the following categories will be summarized:

- < 50 copies/mL
  - < 20 copies/mL
    - < 20 copies/mL Not Detectable
    - < 20 copies/mL Detectable
  - 20 to < 50 copies/mL
- 50 to < 200 copies/mL
- 200 to < 400 copies/mL

- 400 to < 1000 copies/mL
- ≥ 1000 copies/mL

The 95% CI of the proportion of participants with HIV-1 RNA < 50 copies/mL will be provided using the Clopper-Pearson Exact method.

6.2.1. Analysis of CD4+ Cell Count

All CD4+ cell count (/μL) will be summarized using observed, on-treatment data (i.e., data collected up to 1 day after after permanent discontinuation of study drug) for paricipants in the Full Analysis Set for adult participants.

The CD4+ cell count (/μL) and changes from baseline will also be summarized by visit for adult participants using descriptive statistics.

6.2.2. Analysis of CD4%

All CD4% will be summarized using observed, on-treatment data (i.e., data collected up to 1 day after permanent discontinuation of study drug) for adult paricipants in the Full Analysis Set.

The CD4% and change from baseline will also be summarized by visit for adult participants using descriptive statistics.

6.3. Changes From Protocol-Specified Efficacy Analyses

The change from baseline in CD4+ cell count (/μL) and CD4% was added as efficacy endpoints for analysis in this SAP.

7. SAFETY ANALYSES

Safety data will be summarized for the adult participants in the Safety Analysis Set, as well as neonate participants in the Neonate Safety Analysis Set, respectively. This section applies to both adult and neonate participants unless otherwise specified. However, treatment emergent definitions in this section only applies to adult participants.

For adult participants, all safety data collected up to 30 days after permanent discontinuation of study drug will be summarized, unless specified otherwise. For neonate participants, all AEs, deaths, lab abnormalities will be included and summarized.

All safety data will be included in data listings.

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the current version of the MedDRA. System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) will be provided in the AE dataset.

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1, 2, 3, or 4 according to toxicity criteria specified in the protocol. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings.

7.1.3. Relationship of Adverse Events to Study Drug

Study drug related AEs are those for which the investigator selected "Related" on the AE case report form (CRF) to the question of "Related to Study Treatment." Relatedness will always default to the investigator's choice, not that of the medical monitor. 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 from that captured on the CRF.

7.1.4. Relationship of Adverse Events to Study Procedure

Study procedure related AEs are those for which the investigator selected "Yes" on the AE CRF to the question of "Related to Study Procedures." Relatedness will always default to the investigator's choice, not that of the medical monitor. Events for which the investigator did not record relationships to study procedure will be considered related to study procedure. However, by-subject data listings will show the relationship as missing from that captured on the CRF.

7.1.5. Serious Adverse Events

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

7.1.6. Treatment-Emergent Adverse Events

7.1.6.1. 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 study drug.
- Any AEs leading to premature discontinuation of study drug.

This definition only applies to adult participants. All AEs for neonate participants will be reported.

7.1.6.2. Incomplete Dates

This section only applies to adult participants.

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,
- 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 marked as ongoing or 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.

7.1.7. Summaries of Adverse Events and Deaths

Summaries of AEs and deaths will be provided for adults CCI analysis separately using the Safety Analysis Set CCI , respectively. For adults analysis, only TEAE will be included. CCI

7.1.7.1. Treatment-emergent Adverse Events for adult participants

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

The number and percentage of participant who experienced at least 1 TEAE will be provided and summarized by SOC, HLT and PT:

- TEAEs

For the AE categories describe below, summaries will be provided by SOC and PT:

- TEAEs with Grade 3 or higher
- TEAEs with Grade 2 or higher
- TE treatment-related AEs
- TE treatment-related AEs with Grade 3 or higher
- TE treatment-related AEs with Grade 2 or higher
- TE SAEs
- TE treatment-related SAEs
- TEAEs leading to premature discontinuation from study drug
- TEAEs leading to premature discontinuation from study (if applicable)
- TEAEs leading to death (i.e., outcome of death, if applicable)
- All deaths
- Treatment-emergent deaths

A brief, high-level summary of AEs described above will be provided by the number and percentage of participants who experienced the above AEs. Treatment-emergent deaths observed in the study will be also included in this summary.

Treatment-emergent death refers to deaths that occurred between the first dose date and the last dose date plus 30 days (inclusive).

Multiple events will be counted only once per participant 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. For

summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual participant during the study.

In addition to the above summary tables, all TEAEs, TE SAEs, TE treatment-related AEs, and TE treatment-related SAEs will be summarized by PT only, in descending order of total frequency.

In addition, data listings will be provided for adults for the followings:

- All AEs, indicating whether the event is treatment emergent
- All SAEs
- All deaths
- All AEs leading to premature discontinuation of study drug (this only applies to adult participants)
- All AEs leading to premature discontinuation of study

7.1.7.2. Adverse Events for neonate participants

A brief, high-level summary of the number and percentage of neonate participants who experienced at least 1 AE in the categories describes below will be provided. All deaths observed in the study will also be included in this summary.

The number and percentage of participant who experienced at lease 1 AE will be provided and summarized by SOC, HLT and PT:

- AEs

For the AE categories describe below, summaries will be provided by SOC and PT:

- AEs with Grade 3 or higher
- AEs with Grade 2 or higher
- SAEs
- AEs leading to premature discontinuation from study (if applicable)
- AEs leading to death (i.e., outcome of death, if applicable)
- All Death

Multiple events will be counted only once per participant 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. For summaries by severity grade, the most severe grade will be used for those AEs that occurred more than once in an individual participant during the study.

In addition to the above summary tables, all AEs and SAEs will be summarized by PT only, in descending order of total frequency.

In addition, data listings will be provided for adults for the following:

- All AEs
- All SAEs
- All Deaths
- All AEs leading to premature discontinuation of study treatment or study.

7.1.8. Additional Analysis of Adverse Events

7.1.8.1. A Stage 3 Opportunistic Illnesses in HIV

On an ongoing basis, AEs will be reviewed for events that might meet the definition of stage 3 opportunistic illnesses in HIV that are indicative of an AIDS-defining diagnoses (see Protocol Appendix 5). The Gilead medical monitor will review the possible stage 3 opportunistic illnesses and approve the events that meet the definition. Events that meet the stage 3 opportunistic illness definition of an AIDS-Defining Diagnosis will be listed.

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set and Neonate Safety Analysis Set. The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7.

A by-subject listing for laboratory test results will be provided by participant ID number and visit in chronological order for hematology, chemistry, and urinalysis (as applicable) separately. Values falling outside of the reference range and/or having a severity grade of 1 or higher on the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities will be flagged in the data listings, as appropriate.

7.2.1. Summaries of Numeric Laboratory Results

For Adult participants analysis, summaries will include data collected up the the last dose of study drug plus 30 days for participants who have permanently discontinued study drug.

Descriptive statistics will be provided for each laboratory test specified in the study protocol as follows:

- Baseline values
- Values at each postbaseline analysis window
- Change from baseline at each postbaseline analysis window

A baseline laboratory value will be defined as the last nonmissing value obtained on or prior to the date of first dose of study drug for Adult participants.

Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value. The mean, median, Q1, Q3, minimum, and maximum values will be displayed to the reported number of digits; SD values will be displayed to the reported number of digits plus 1.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.7.

For Neonate participants analysis, laboratory results will be based on nominal visits and change from baseline does not apply to Neonate analysis, i.e. only baseline values and values at week 4-8 visit will be presented. Languages about change from baseline do not apply to neonate participants analysis.

7.2.2. Graded Laboratory Values

The Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities will be used for assigning toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (i.e., increased, decreased) will be presented separately.

If there is any laboratory toxicity grading scale overlapping with the normal reference ranges (eg, Grade 1 scale overlaps with normal reference ranges), laboratory values that are within the normal range will be Grade 0, except for lipid tests.

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point, up to 30 days after permanent discontinuation of study drug. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment-emergent. This definition only applies to adult participants. CCI [redacted]

Fasting glucose and nonfasting glucose (including glucose results without a known fasting status) are graded based on different grading scales as specified in the protocol. Treatment-emergent laboratory abnormalities will be summarized for fasting glucose. Maximum postbaseline grade (instead of treatment-emergent grade) for nonfasting glucose (including glucose results without a known fasting status) will be summarized. Regarding nonfasting glucose, since it was not assessed at baseline visit for most of the participants and therefore, whether an abnormality is treatment-emergent or not cannot be determined for these participants.

Both urine RBC based on microscopic examination, labeled as Hematuria (Quantitative), and urine blood based on a dipstick, labeled as Hematuria (Dipstick), are assessed routinely and assigned a toxicity grade in this study. Urine RBC based on microscopic examination will be presented in laboratory toxicity summary tables and listings while urine blood based on a dipstick will be presented in the listings only.

7.2.2.2. Summaries of Laboratory Abnormalities

Laboratory data that are categorical will be summarized using the number and percentage of participants in the study with the given response at baseline and each scheduled postbaseline time point visit.

The following summary (number and percentage of participants) for treatment-emergent laboratory abnormalities will be provided by lab test; participants will be categorized according to the most severe postdose abnormality grade for a given lab test:

- Graded laboratory abnormalities
- Grade 3 or 4 laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of participants with any nonmissing postbaseline values up to 30 days after last dosing date, CCI [redacted] Treatment emergent definition only applies to adult participants. CCI [redacted].

A by-subject listing of graded laboratory abnormalities will be provided by participant ID number and visit in chronological order.

7.2.3. Liver-Related Laboratory Evaluations

Liver related laboratory evaluations only applies to analysis on adult participants.

Liver-related abnormalities after initial study drug dosing will be examined and summarized using the number and percentage of participants who were reported to have the following laboratory test values for postbaseline measurements:

- Aspartate aminotransferase (AST): (a) > 3 times of the upper limit of reference range (ULN), (b) > 5 × ULN, (c) > 10 × ULN, (d) > 20 × ULN
- Alanine aminotransferase (ALT): (a) > 3 × ULN, (b) > 5 × ULN, (c) > 10 × ULN, (d) > 20 × ULN
- AST or ALT: (a) > 3 × ULN, (b) > 5 × ULN, (c) > 10 × ULN, (d) > 20 × ULN
- Total bilirubin: (a) > 1 × ULN, (b) > 2 × ULN
- Alkaline phosphatase (ALP) > 1.5 × ULN
- AST or ALT > 3 × ULN and total bilirubin: (a) > 1.5 × ULN, (b) > 2 × ULN
- AST or ALT > 3 × ULN and total bilirubin > 2 × ULN and ALP < 2 × ULN

The summary will include data from all postbaseline visits up to 30 days after the last dose of study drug for adults. For individual laboratory tests, participants will be counted once based on the most severe postbaseline value. For both the composite endpoint of AST or ALT and total bilirubin, and the composite endpoint of AST or ALT, total bilirubin, and ALP, participants will be counted once when the criteria are met at the same postbaseline visit date. The denominator is the number of adult participants in the Safety Analysis Set as applicable with nonmissing postbaseline value of the tests in evaluation at the same postbaseline visit date. Participants with AST or ALT > 3 × ULN will also be listed.

In addition, baseline, postbaseline, and change from baseline in AST, ALT, ALP, and total bilirubin will be summarized by visit using descriptive statistics.

7.2.4. Renal-Related Laboratory Evaluations

Renal related laboratory evaluations only applies to analysis on adult participants.

7.2.4.1. Serum Creatinine and $eGFR_{CG}$

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

7.3. Body Weight, Height, BMI, and Vital Signs

Descriptive statistics will be provided for body weight and vital signs (for both adults and CCI pulse, respiration rate, body temperature; for adults only: BMI, systolic blood pressure, diastolic blood pressure) as follows:

- Baseline values
- Values at each postbaseline analysis window
- Change from baseline to each postbaseline analysis window

CCI [redacted]

A baseline value for adult participants will be defined as the last nonmissing value obtained on or prior to the date of first dose of study drug. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value. In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.7.3. No formal statistical testing is planned.

A by-subject listing of vital signs will be provided by subject ID number and visit in chronological order. In the same listing, a by-subject listing of body weight, height, and BMI will be provided. For Neonate participants, Apgar scoring (at 5 and 10 minutes after delivery) and Anthropometric measures (Head circumference, weight and length at birth and once between 4 to 8 weeks of age) will also be listed.

7.4. Prior and Concomitant Medications

7.4.1. Nonstudy Drug Antiretroviral Medications

Any nonstudy drug ARV medications used prior to, during, or after the study (if collected) will be coded using the Gilead-modified World Health Organization (WHO) Drug Dictionary for ARV medications. The WHO preferred drug name and drug code will be attached to the clinical database. All nonstudy drug ARV medications will be listed. No inferential statistics will be provided.

7.4.2. Concomitant Non-ARV Medications

Concomitant non-ARV medications (i.e., medications other than study drug that are taken while receiving study drug) will be coded using the WHO Drug Dictionary. The WHO preferred drug name and drug code will be attached to the clinical database.

For neonate participants, all medications after birth will be considered as concomitant. For adult participants, if the start or stop date of non-ARV medications is incomplete, the month and year (or year alone, if month is not recorded) of the start or stop date will be used to determine

whether the non-ARVs are concomitant or not. The medication is concomitant if the month and year of the start or stop (or year of the start or stop, if month is not recorded) of the medication does not meet either of the following criteria:

- The month and year of start of the medication is after the date of the last dose of study drug
- The month and year of stop of the medication is before the date of the first dose of study drug

If the start and stop date of non-ARV medications are complete, the start date is not after last dose date and the stop date is not before first dose date, or the non-ARV medications are marked as ongoing and start date is on or before last dose date, the non-ARV medications are concomitant.

Summaries of non-ARV concomitant medications will be provided for the safety analysis set. Participants with any non-ARV concomitant medications will be listed. No inferential statistics will be provided.

7.5. Electrocardiogram Results

A by-subject listing for adult participants for ECG assessment results will be provided by participant ID number and time point in chronological order.

7.6. Other Safety Measures

No additional safety measures are specified in the protocol.

7.7. Changes From Protocol-Specified Safety Analyses

There are no deviations from the protocol-specified safety analyses.

8. PHARMACOKINETIC EVALUATION/ANALYSIS

8.1. Estimation of Pharmacokinetic Parameters

Pharmacokinetic (PK) parameters will be estimated using Phoenix WinNonlin® software using standard noncompartmental methods. The linear up/log down rule will be used in conjunction with the appropriate noncompartmental model, with input values for dose level, dosing time, PK 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.

For area under the curve (AUC), samples below the limit of quantitation (BLQ) of the bioanalytical assays occurring 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 in WinNonlin. The nominal time point for a key event (eg, urine collection) or dosing interval (τ) may be used to permit direct calculation of AUC over specific time intervals. The appropriateness of this approach will be assessed by the PK scientist on a profile-by-profile basis.

Pharmacokinetic parameters such as Vz/F and $t_{1/2}$ are dependent on an accurate estimation of the terminal elimination phase of drug. The appropriateness of calculating these parameters will be evaluated upon inspection of PK data on a profile-by-profile basis by the PK scientist. For instance, the model estimates of Vz/F and $t_{1/2}$ may be found not accurate enough for some participants (i.e., adjusted R-squared < 0.8). In this case, the Vz/F and $t_{1/2}$ for those participants will not be used to compute the summary statistics.

A listing of individual participant data for the determination of plasma half-life and corresponding correlation coefficient will be provided for each analyte, including intensive PK sampling day, number of data points in regression, start time, end time, and correlation coefficient.

8.2. Pharmacokinetic Parameters

Pharmacokinetic parameters will be generated for all adult participants for whom parameters can be derived as applicable. CCI [redacted] (see Table 8-1).

Table 8-1. Study Treatments and Associated Analytes

Analysis population	Treatment	Analyte(s)
Adults	B/F/TAF	BIC, TAF, FTC, TFV-DP
CCI [redacted]		

Unbound plasma BIC and TAF concentrations and PK parameters will be analyzed using descriptive statistics as applicable.

The analytes and parameters presented in Table 8-2 will be used to evaluate the PK objectives of the study for adult participants. No parameters will be calculated for TFV-DP, due to one timepoint sampling per intensive PK visit [redacted]. The PK parameters to be estimated in this study are listed and defined in the Pharmacokinetic Abbreviations section.

Table 8-2. Pharmacokinetic Parameters for Each Analyte

Analysis population	Analytes	Sample Matrix	Parameters
Adults	BIC	PLASMA	AUC_{tau}, Unbound AUC_{tau}, C_{tau}, Unbound C_{tau}, C_{max}, Unbound C_{max}, AUC_{last}, C_{last}, T_{max}, T_{last}, CL_{ss}/F, V_z/F, $t_{1/2}$
Adults	TAF	PLASMA	AUC_{tau}, Unbound AUC_{tau}, C_{max}, Unbound C_{max}, AUC_{last}, C_{last}, T_{max}, T_{last}, CL_{ss}/F, V_z/F, $t_{1/2}$
Adults	FTC	PLASMA	AUC_{tau}, C_{tau}, C_{max}, AUC_{last}, C_{last}, T_{max}, T_{last}, CL_{ss}/F, V_z/F, $t_{1/2}$
Neonate	BIC	PLASMA	$t_{1/2}$ (if applicable)
Neonate	TAF	PLASMA	$t_{1/2}$ (if applicable)

8.3. Statistical Analysis Methods

8.3.1. General Considerations

Individual participant concentration data and individual participant PK parameters for BIC, TAF, FTC, and TFV-DP will be listed and summarized using descriptive statistics by visit day, as applicable. Summary statistics (numbers of participants, mean, SD, coefficient of variation [%CV], median, minimum, maximum, Q1, and Q3) will be presented for both individual participant concentration data by time point and visit day, and individual participant PK parameters by visit day. Moreover, the geometric mean, 95% confidence interval (CI), and the mean and SD of the natural log-transformed values will be presented for individual participant PK parameter data.

Protein binding information for BIC and TAF will be listed and summary statistics (numbers of participants, mean, SD, coefficient of variation [%CV], median, minimum, maximum, Q1, and Q3) will be presented for protein bound and unbound fraction (%) by visit for each analyte, respectively. Protein binding data will be used to calculate unbound plasma concentrations and unbound PK parameters for BIC and TAF.

Individual concentration data listings and summaries will include all participants with concentration data. The sample size for each time point will be based on the number of participants with nonmissing concentration data at that time point. The number of participants with concentration BLQ will be presented for each time point. Handling of BLQ data is specified in Section 3.6.

Individual PK parameter data listings and summaries will include all participants for whom PK parameter(s) can be derived. The sample size for each PK parameter will be based on the number of participants with nonmissing data for that PK parameter.

Comparisions between individual PK parameters between pregnancy and postpartum will be listed and summarized using descriptive statistics.

The following tables will be provided for each analyte by visit as applicable:

- Individual participant plasma and PBMC concentration data and summary statistics
- Individual participant PK parameters and summary statistics
- Individual participant bound and unbound fractions of BIC or TAF and summary statistics
- Individual participant cord blood to maternal blood plasma concentration ratios and summary statistics (BIC or TAF only)

The following figures will be provided for each analyte including unbound plasma BIC and unbound plasma TAF by visit day as applicable:

- Individual participant concentration data versus time (on linear and semilogarithmic scales)
- Mean (± SD) concentration data versus time (on linear and semilogarithmic scales)
- Median (Q1, Q3) concentration data versus time (on linear and semilogarithmic scales)
- Spaghetti plots of PK parameters versus time on linear scale
- Boxplots of PK parameters versue time on linear scale

Individual, mean, and median postdose concentration values that are ≤ LLOQ will not be displayed in the figures and remaining points connected.

The following listings will be provided:

- Plasma and PBMC (if applicable) PK sampling details by participant, including procedures, differences in scheduled and actual draw times, and sample age

- Individual data on determination of plasma half-life and corresponding regression correlation coefficient for each analyte.

Plasma concentrations and PK parameters will be listed and summarized using descriptive statistics by visit for maternal and neonate PK analysis sets, respectively.

8.3.2. Statistical Methodology

Adults:

The statistical comparisons of the natural log-transformed PK parameters for each analyte of interest will be performed. The statistical modeling will be based on the PK Analysis Set for the analyte under evaluation. For each analyte, all participants with available data for the PK parameter under evaluation will be included in the modeling.

Comparisons of interest are shown in Table 8-3.

Table 8-3. Statistical Comparisons for Pharmacokinetic Analyses

Analytes	PK Parameter	Comparison		No Effect Boundary for Lower Bound of 90% CI
		Test	Reference	
BIC	AUC_{tau} C_{max} C_{tau} Unbound AUC_{tau} Unbound C_{max} Unbound C_{tau}	Second Trimester	Week 6 post-partum	> 50%
		Second Trimester	Week 12 post-partum	> 50%
		Third Trimester	Week 6 post-partum	> 50%
		Third Trimester	Week 12 post-partum	> 50%
TAF	AUC_{tau} C_{max} Unbound AUC_{tau} Unbound C_{max}	Second Trimester	Week 6 post-partum	> 50%
		Second Trimester	Week 12 post-partum	> 50%
		Third Trimester	Week 6 post-partum	> 50%
		Third Trimester	Week 12 post-partum	> 50%
FTC	AUC_{tau} C_{max} C_{tau}	Second Trimester	Week 6 post-partum	> 50%
		Second Trimester	Week 12 post-partum	> 50%
		Third Trimester	Week 6 post-partum	> 50%
		Third Trimester	Week 12 post-partum	> 50%

For each analyte and each PK parameter, a parametric (normal theory) mixed-effects ANOVA model will be fitted to the natural log-transformed values of the PK parameter under evaluation using SAS® PROC MIXED.

The statistical model will include visit as a fixed effect and participant as a random effect. The following sample SAS PROC MIXED code will provide the treatment comparison analysis for BIC analyte and parameter 'AUCtau', and the 90% CI calculations for natural log-transformed PK parameters.

```
proc mixed;
   where analyte='BIC' and param='AUCtau';
   class subjid visit;
   model lnest = visit/ ddfm=kr;
```

```
   random subjid;
   lsmeans visit / diff cl alpha = 0.1;
   ods output Estimates = LS_Diffs LSMeans = LS_Means CovParms = MSE;
run;
```

The ESTIMATE statement will be used to produce the point estimate and the corresponding 90% CI of the difference in PK parameters of interest on a logarithmic scale. The test-to-reference ratio and associated 90% CI will be calculated by taking the exponention of the point estimate and the corresponding lower and upper limits, which is consistent with the two 1-sided tests approach {U.S. Department of Health and Human Services 2015}.

Individual participant estimates of pharmcokinetic parameters and comparisons with fold changes (defined as the ratio between the two quantities at 2 visits) will be listed and summarized by visits using descriptive statistics.

Neonate:

Plasma concentration of BIC and TAF will be summarized by nominal sampling time using descriptive statistics. The PK parameters such as terminal half-life of BIC and TAF will be calculated and summarized if possible.

The cord blood to maternal blood plasma concentrations ratio for BIC and TAF will be calculated and summarized. If "BLQ" is present, no ratio need to be generated for that record.

8.4. Sensitivity Analysis

Sensitivity analysis may be conducted for the key PK analyses if the PK scientist identifies PK data as questionable. The sensitivity analysis will exclude specific data from analyses, if appropriate. If a sensitivity analysis is deemed necessary, a listing of the PK parameter(s) data being excluded, with associated reason(s) provided by the PK scientist, will be generated.

9. REFERENCES

U. S. Department of Health and Human Services, Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER). Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment. Guidance for Industry. Silver Spring, MD. November, 2015.

10. SOFTWARE

SAS® Software Version 9.4. (SAS Institute Inc., Cary, NC, USA) is used for all programming of tables, listings, and figures.

nQuery Advisor® Version 8.5.1 (Statistical Solutions, Cork, Ireland.) is used for sample size and power calculation.

Phoenix WinNonlin® 8.3 (Pharsight Corporation, Princeton, NJ, USA) is used for pharmacokinetic/pharmacodynamic (PK/PD) analyses.

11. SAP REVISION

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

APPENDICES

Appendix 1. Maternal and Neonatal Study Procedures Tables

Maternal Study Procedures Table

Study Procedure	Screening	Day 1	Visits before the delivery		Delivery Visit[j]	Post-partum Visit		30-Day Follow-up Visit	ESDD
			Week 4	Weeks 8, 12, 16, 20 & 24 (dependent on time of enrollment)[a]		Week 6	Week 12		
Written Informed Consent	X								
Medical History	X								
Complete Physical Examination[b]	X	X	X	X[b]		X	X		X
ECG	X								
Symptom-directed Physical Examination[c]				X[c]				X	
Vital Signs (including weight)	X	X	X	X		X	X	X	X
Height	X								
Laboratory Assessments[d]	X	X		X[d]		X	X	X	X
Maternal alfa-fetoprotein level	X								
Urine Pregnancy Test[e]						X	X	X	X

Study Procedure	Screening	Day 1	Visits before the delivery		Delivery Visit[j]	Post-partum Visit		30-Day Follow-up Visit	ESDD
			Week 4	Weeks 8, 12, 16, 20 & 24 (dependent on time of enrollment)[a]		Week 6	Week 12		
eGFRf	X	X		Xe		X	X		
HIV-1 RNA	X	X	X	X	X	X	X	X	X
Whole Blood Sample for HIV-1 Genotypingg	X								
CD4+ cell count	X	X					X		
HBV and HCV Testing	X								
Ultrasoundh	X								
Intensive PK Sample Collectioni, j			X	X		X	X		
Sparse PK Sample Collectionk					X				
Plasma Storage Sample		X	X	X		X	X		X
CCI									
Drug and Alcohol Screening	X	X							
Adverse Event and Concomitant Medication Review	X	X	X	X	X	X	X	X	X
Date of Delivery					X				
Pregnancy outcome					X				
B/F/TAF Dispensation		X	X	X	X	X			
B/F/TAF Accountability			X	X		X	X		X

a. After completion of the Week 4 visit, participants will be required to come back for a study visit every 4 weeks (Weeks 8, 12, 16, 20, 24 dependent on time of enrollment and time of delivery). Study visits may be completed within ± 2 days of protocol-specified visit date.
b. A complete physical examination will be completed at Day 1, Week 4, Week 12 and Weeks 6 and 12 post-partum visits, and at the ESDD visit.
c. A symptom directed physical examination will be completed at Weeks 8, 16, 20 and 24 visits and at the 30-Day Follow-up Visit.
d. Clinical laboratory assessments include hematology, chemistry and urinalysis which will be completed at Screening, Day 1, Weeks 12 and 24, Weeks 6 and 12 post-partum visits, 30-Day Follow-up Visit and ESDD Visit.
e. Urine pregnancy testing will be completed at the ESDD if it is clinical appropriate and the participant is in the post-partum phase of the study.
f. eGFR will be calculated at Screening, Day 1, Weeks 12 and 24, and Weeks 6 and 12 post-partum visits.
g. Sample may be collected at Screening OR Day 1.
h. Ultrasound should be completed prior to the Day 1 visit. An ultrasound completed prior to the screening visit is acceptable.
i. Before delivery, Intensive PK sample collection will be completed after participant administers B/F/TAF for at-least 3 weeks. For participants enrolled during the second trimester, iPK sample collection will be completed at or between 20 to 28 weeks of gestation and at or between 30 to 38 weeks of gestation. For participants enrolled during the third trimester, iPK sample collection will be completed at or between 30 to 38 weeks of gestation.
j. After delivery, iPK sample collection will be completed at Week 6 and Week 12 post-partum visits.
k. A single maternal blood sample and an umbilical cord sample after cord clamping will be collected at the time of delivery (Delivery Visit).
l. [redacted]
m. The day of delivery will be considered as the Delivery Visit for study purposes.

Neonatal Study Procedures Table

Study Procedure	Delivery Visit	4-8 Weeks of age
Complete Physical Examination	X	X
Vital signs	X	X
Apgar score[n]	X	
Anthropometric measures[o]	X	X
HIV-1 RNA and Safety Assessments[p]	X	X
Sparse PK Sample Collection[q]	X	

n. Apgar score will be collected if it is recorded at the time of birth per standard of care
o. Head circumference, weight and length at birth and 4-8 weeks of age will be collected
p. HIV-1 RNA and safety assessments which includes CBC, LFTs (ALT, AST, total and direct bilirubin) may be completed using the sparse PK samples collected on the day of birth, if there is sufficient volume. If blood volume is insufficient, results from testing performed per standard of care will be obtained. HIV-1 RNA and safety assessments will also be completed at 4-8 weeks of age if possible or results from testing performed per standard of care will be obtained.
q. Sparse PK blood samples will be collected at the following time points, if possible: at or between 0 to < 2 hours, 2 to < 3 hours, 3 to 8 hours, 18 to 28 hours, 36 to 72 hours, and 5 to 7 days after birth. These time points may vary based on birth weight, additional instructions will be included in the Pharmacokinetic Sample Collection and Processing Instructions Manual.

Appendix 2. Adverse Events of COVID-19 and Suspected COVID-19 Infection

An adverse event record will be flagged as adverse events for COVID-19 and Suspected COVID-19 infection if its MedDRA PT is included in the pre-specified PT list, which includes all PTs from the narrow search of the following COVID-19 SMQs under MedDRA v25.0 provided by Gilead GLPS (search name: COVID-19 (SMQ) – Narrow) and reviewed by Gilead medical monitors.

	SMQ Source
AEs for COVID-19 and Suspected COVID-19 infection	COVID-19 (SMQ) (Narrow Scope)

Appendix 3. Data Collection of COVID-19 Data

This appendix describes the clinical trial site collection of COVID-19 data pertaining to missed/virtual visits and the data processing algorithm that will be used to determine which visits are missing and which visits are virtual.

Data Collection

A COVID-19 supplement to the eCRF Completion Guidelines (CCG) was provided by Clinical Data Management to instruct clinical trial sites with data entry expectations pertaining to scenarios related to the COVID-19 pandemic. If a visit was missed, sites were instructed to enter "Visit missed due to COVID-19" and if an in-person visit was conducted virtually, sites were instructed to enter "Virtual visit due to COVID-19".

Determination of Missed and Virtual Visits

Natural Language Processing (NLP) will be used to search the CRF comment fields to identify instances of "COVID-19", "Virtual", or synonyms (see Table X-1). The search terms will be maintained in a global lookup table and can be modified to tune the NLP model. Any comments with COVID-19 search terms, "Missed visit" or "Virtual visit" will be assigned as follows:

i. If COVID-19 terms are identified through NLP and the visit date is missing, then result is "Missed Visit"
ii. If COVID-19 and Virtual terms are identified through NLP for a visit, then result is "Virtual Visit". When there are multiple records for the same participant and the same visit, if one record could be categorized as "Virtual Visit", all records associated with this participant and this visit will be categorized as "Virtual Visit"
iii. Otherwise result is missing

Table X-1. Examples of Searching Terms for "COVID-19" and "Virtual" Used to Identify Missed and Virtual Visits

Search Terms for "COVID-19"	Search Terms for "Virtual"
COVID19	VIRTUAL
CORONA	TELEMED
CORONAVIRUS	TELEHEALTH
PANDEMIC	TELEPHONE
OUTBREAK	REMOTE
CRISIS	TELEMEDICINE
LOCKDOWN	TELECONSULTATION
QUARANTINE	TELEPHONICALLY
SHELTER	PHONE
	HOME VISIT
	ZOOM
	SKYPE

Appendix 4. Programming Specification

1) Body mass index (BMI)

BMI will be calculated only at baseline as follows for adults:

- BMI = (weight [kg]) / (height [meters]^2)

Baseline height and weight will be used for this calculation. BMI will not be populated for neonate participants.

2) Calcium Corrected for Albumin

Calcium corrected for albumin will be calculated and summarized for the study. The following formula will be used when both serum calcium and albumin results for a given blood drawn are available and serum albumin value is < 4.0 g/dL.

- Calcium corrected for albumin (mg/dL) = serum calcium (mg/dL) + 0.8 × (4.0 – albumin (g/dL)).

Toxicity grading for calcium will be applied based on the corrected values.

3) Estimated GFR

The following formula will be used to calculate the estimated glomerular filtration (eGFR) rate according to the Cockcroft Gault formula ($eGFR_{CG}$):

- eGFR(CG) (mL/min) = [(140 – age (yrs)) × weight [kg]) × (0.85 if female)] / (SCr (mg/dL) × 72),

where weight is total body mass in kilograms, and SCr is serum creatinine.

4) Graded Laboratory Abnormalities Summary

The following labels will be used for treatment-emergent laboratory abnormalities and treatment-emergent Grade 3 or 4 laboratory abnormalities summary tables and listings:

Battery	Lab Test Label Used in l-labtox Listing	Toxicity Direction	Lab Test Label Used in t-labtox Table
Hematology	Hemoglobin	Decrease	Hemoglobin (Decreased)
	Neutrophils	Decrease	Neutrophils (Decreased)
	Platelets	Decrease	Platelets (Decreased)
	WBC	Decrease	WBC (Decreased)
Chemistry	Albumin	Decrease	Albumin (Decreased)
	Alkaline Phosphatase	Increase	Alkaline Phosphatase (Increased)
	ALT	Increase	ALT (Increased)
	Amylase	Increase	Amylase (Increased)
	AST	Increase	AST (Increased)
	Bicarbonate	Decrease	Bicarbonate (Decreased)
	Corrected Calcium	Increase	Corrected Calcium (Hypercalcemia)
	Corrected Calcium	Decrease	Corrected Calcium (Hypocalcemia)
	Creatine Kinase (CK)	Increase	Creatine Kinase (Increased)
	Creatinine	Increase	Creatinine (Increased)
	GGT	Increase	GGT (Increased)
	Lipase	Increase	Lipase (Increased)
	Magnesium	Decrease	Magnesium (Hypomagnesemia)
	Phosphate	Decrease	Phosphate (Hypophosphatemia)
	Serum Glucose (Fasting)	Increase	Serum Glucose (Fasting, Hyperglycemia)
	Serum Glucose (Fasting)	Decrease	Serum Glucose (Fasting, Hypoglycemia)
	Serum Glucose (Nonfasting)	Increase	Serum Glucose (Nonfasting, Hyperglycemia)
	Serum Glucose (Nonfasting)	Decrease	Serum Glucose (Nonfasting, Hypoglycemia)
	Serum Potassium	Increase	Serum Potassium (Hyperkalemia)
	Serum Potassium	Decrease	Serum Potassium (Hypokalemia)
	Serum Sodium	Increase	Serum Sodium (Hypernatremia)
	Serum Sodium	Decrease	Serum Sodium (Hyponatremia)
	Total Bilirubin	Increase	Total Bilirubin (Hyperbilirubinemia)
	Total Cholesterol (Fasting)	Increase	Total Cholesterol (Fasting, Hypercholesterolemia)

Battery	Lab Test Label Used in l-labtox Listing	Toxicity Direction	Lab Test Label Used in t-labtox Table
	Triglycerides (Fasting)	Increase	Triglycerides (Fasting, Increased)
	LDL (Fasting)	Increase	LDL (Fasting, Increased)
	Urea Nitrogen (BUN)	Increase	Urea Nitrogen (Increased)
	Uric Acid	Increase	Uric Acid (Hyperuricemia)
	Uric Acid	Decrease	Uric Acid (Hypouricemia)
Urinalysis	Urine Blood	Increase	Urine RBC (Hematuria, Quantitative or Dipstick)*
	Urine Glucose	Increase	Urine Glucose (Glycosuria)
	Urine Protein	Increase	Urine Protein (Proteinuria)
	Urine RBC (Quantitative)	Increase	Urine RBC (Hematuria, Quantitative or Dipstick)*

* Both urine RBC based on microscopic examination, labeled as Hematuria (Quantitative), and urine blood based on a dipstick, labeled as Hematuria (Dipstick), are assessed routinely and assigned a toxicity grade in this study. Urine RBC based on microscopic examination will be presented in laboratory toxicity summary tables and listings while urine blood based on a dipstick will be presented in the listings only.

5) Unbound plasma BIC and TAF concentration

Unbound plasma BIC and TAF concentration (ng/mL) will be computed using plasma BIC and TAF concentration (ng/mL) and the protein unbound fraction:

- Unbound plasma BIC or TAF concentration (ng/mL) = plasma concentration of BIC or TAF (ng/mL) × protein unbound fraction.

6) Unit conversion for TFV-DP in CCI

The molecular weight for TFV-DP is 447.17 g/mol (https://pubchem.ncbi.nlm.nih.gov/compound/tenofovir-diphosphate).

Given the CCI specimen is set to a contant value of 5000 million cells/mL in the test,

- 1 ng/million cells TFV-DP from the CCI sample is equivalent to $\frac{0.001\ \mu g/\text{million cells} \times 5000\ \text{million cells/mL}}{447.17\ g/mol} = \frac{5000\ \mu mol/L}{447.17} =$ 11.1814 µmol/L.

CCI

SAP-Final-GS-US-380-5310-v1.0

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Biostatistics eSigned	16-Nov-2022 05:01:36
PPD	Project Team Leader eSigned	16-Nov-2022 16:31:46
PPD	Clinical Pharmacology eSigned	16-Nov-2022 18:34:16