Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan Amendment 1 for An Open-label, Randomized, Single dose, Crossover, Pivotal Bioequivalence Study of Fixed-dose Combination Tablets of Dolutegravir and Lamivudine versus Dolutegravir and Lamivudine single entities and Food Effect Assessment in Healthy Volunteers
Compound Number	:	GSK3515864 (GSK1349572+GR109714)
Effective Date	:	28-AUG-2017

Description :

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 204994
- This RAP is intended to describe the safety, pharmacokinetics (PK), and tolerability analyses required for the study.
- This version of the RAP includes amendment 1 to the originally approved RAP.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

Author's Name and Functional Area:

PPD (Clinical Statistics, PAREXEL)	22-AUG-2017

The Clinical Statistician (or designee) will give final approval:

PPD (Clinical Statistics, GSK)	23-AUG-2017

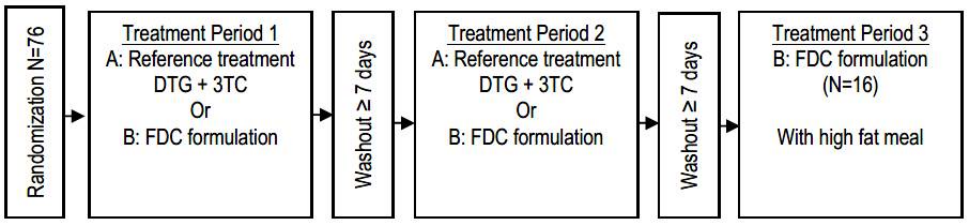
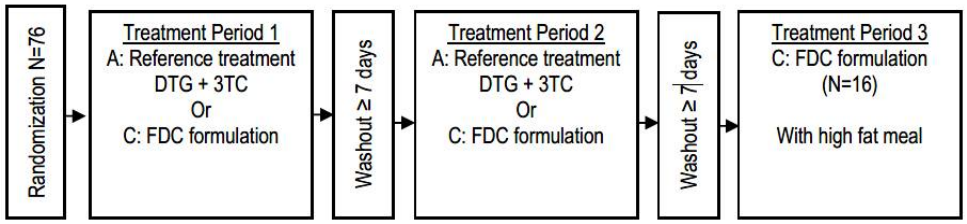
Revision Chronology

Date	**Version**
26-JUL-2017	Original
28-AUG-2017	Amendment No. 1
Amendment 1 provides clarity that a similar preliminary PK analysis as was conducted following Part 1, will also be performed for Part 2.	

TABLE OF CONTENTS

PAGE

1. REPORTING & ANALYSIS PLAN SYNOPSIS

Overview	Key Elements of the Reporting and Analysis Plan
Purpose	The purpose of this reporting and analysis plan (RAP) is to describe the planned analyses and output to be included in the Clinical Pharmacology Study Report for Protocol 204994
Protocol	This RAP is based on the original protocol (Dated: 12-JAN-2017) of study GSK204994 (GSK Document No.: 2016N286215_00) and protocol amendment 1 (Dated: 07-FEB-2017) of study GSK204994 (GSK Document No.: 2016N286215_01)
Primary Objective	To evaluate the bioequivalence (BE) of fixed-dose combination (FDC) tablet formulation(s) of DTG 50 mg and 3TC 300 mg versus co-administration of the separate tablet formulations of DTG 50 mg plus 3TC 300 mg, in the fasted state.
Primary Endpoint	Plasma DTG and 3TC $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, and C_{max}.
Study Design	This is a single-center, open-label, randomized, two-part study (if Part 2 is conducted) Part 1, Bioequivalence and Food Effect (FD) with Monolayer FDC Tablet Part 1 of the study will be a randomized, open-label, 2-period, single-dose, crossover study in 76 healthy adult subjects to achieve at least 70 evaluable subjects. The first 16 subjects who complete the first two treatment periods, and consent to continue, will return for a third treatment period and receive a single dose of the FDC tablet formulation administered with a high fat meal.  Part 2, Bioequivalence and Food Effect with Bilayer FDC Tablet Part 2 of the study, incorporating the bilayer FDC formulation, will only be conducted if a suitable formulation is available. Part 2 of the study will be conducted, similarly to Part 1. 
Planned Analyses	• Interim analyses are detailed within Section 3.1. • The final planned analyses will be performed after the completion of the study and final datasets authorization, i.e. when database freeze

Overview	Key Elements of the Reporting and Analysis Plan
	(DBF) is declared.
Analysis Population	• Screening Population • Safety Population • PK Plasma Concentration Population • PK Parameter BE Summary Population • PK Parameter FD Summary Population
Hypothesis	The first two treatment periods of each part of this study are designed to test the BE of FDC tablets of DTG and 3TC (test treatment) relative to co-administered DTG plus 3TC (reference treatment) all under fasting condition: • H(0): μ(test)/μ(reference) < 0.800 or μ(test)/μ(reference) > 1.250, i.e., treatments are not bioequivalent. Versus • H(1): 0.800 ≤ μ(test)/μ(reference) ≤ 1.250 i.e., treatments are bioequivalent. Food Effect: No formal hypothesis will be tested and an estimation approach will be used to evaluate the effect of food on the FDC tablet(s).
Primary Analyses	Following $\log_e$-transformation, $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, C_{max} from the first two treatment periods for BE will be separately analyzed for each analyte using a mixed effects model. Point estimates and their associated 90% confidence intervals (CIs) will be provided for the ratios of PK parameters between test and reference treatments on the original scale.
Secondary Analyses	• PK data will be presented in graphical and/or tabular form and will be summarized descriptively. • Following $\log_e$-transformation, $AUC_{(0-24)}$, C_{24}, CL/F and $t_{1/2}$ from the first two treatment periods for BE, and $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, C_{max}, CL/F, $AUC_{(0-24)}$, C_{24}, $t_{1/2}$ from the third treatment period (food effect) will be analysed similarly using a mixed effects model. • T_{max} and t_{lag} of DTG and 3TC will be separately analyzed with the non-parametric Wilcoxon matched pair method to compute point estimates and associated 90% CIs for the median differences. • Safety data will be presented in tabular format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards. No formal statistical analysis of the safety data will be conducted.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Except for the addition of a similar preliminary PK analysis for Part 2 as was conducted for Part 1, there were no changes or deviations to the originally planned statistical analysis specified in the protocol amendment 1 [Dated: 07-FEB-2017].

2.2. Study Objective(s) and Endpoint(s)

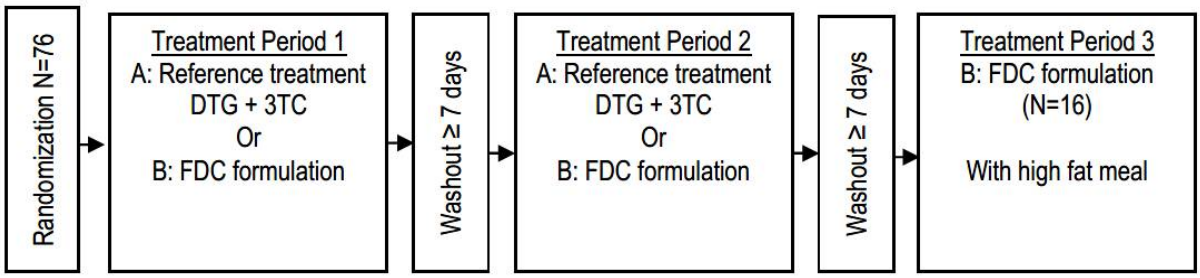
Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
To evaluate the bioequivalence of FDC tablet formulation(s) of DTG 50 mg and 3TC 300 mg versus co-administration of the separate tablet formulations of DTG 50 mg plus 3TC 300 mg, in the fasted state.	Plasma DTG and 3TC $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, and C_{max}.
Secondary Objectives	**Secondary Endpoints**
• To characterize the PK profile of single dose of FDC tablet formulation(s) of DTG 50 mg and 3TC 300 mg versus co-administration of the separate tablet formulations of DTG 50 mg plus 3TC 300 mg, in the fasted state	• Plasma DTG and 3TC t_{lag}, t_{max}, t, $t_{½}$, λz, $\%AUC_{ex}$, $AUC_{(0-24)}$, CL/F and Vz/F, C_t, and C_{24}
• To evaluate the food effect on FDC tablet formulation(s) of DTG 50 mg and 3TC 300 mg	• Plasma DTG and 3TC $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, C_{max}, t_{lag}, t_{max}, t, $t_{½}$, λz, $\%AUC_{ex}$, $AUC_{(0-24)}$, CL/F and Vz/F, C_t, and C_{24}.
• To assess the safety and tolerability from single dose administration of the combination of DTG 50 mg, 3TC 300 mg in healthy volunteers either fasted or with a high fat meal.	• Safety and tolerability parameters as assessed by change from baseline in vital signs (BP and HR), number of subjects with adverse events and toxicity grading of clinical laboratory tests

$AUC_{(0-t)}$= area under the plasma concentration time curve from time zero to the last quantifiable time point
$AUC_{(0-\infty)}$= area under the plasma concentration time curve from time zero to infinity
$AUC_{(0-24)}$= area under the plasma concentration time curve from time zero to 24 hours
$\%AUC_{ex}$=% of $AUC_{(0-\infty)}$ that was extrapolated
C_{max}= maximum observed concentration
t_{max}= time of maximum observed concentration
C_{24}= concentration at 24h post-dose
C_t = last quantifiable concentration
PK = Pharmacokinetic
t = time of last quantifiable concentration
t_{lag}= absorption lag time
λz=apparent elimination rate constant
$t_{1/2}$ = the elimination half-life
CL/F = apparent oral clearance
Vz/F= apparent oral volume of distribution

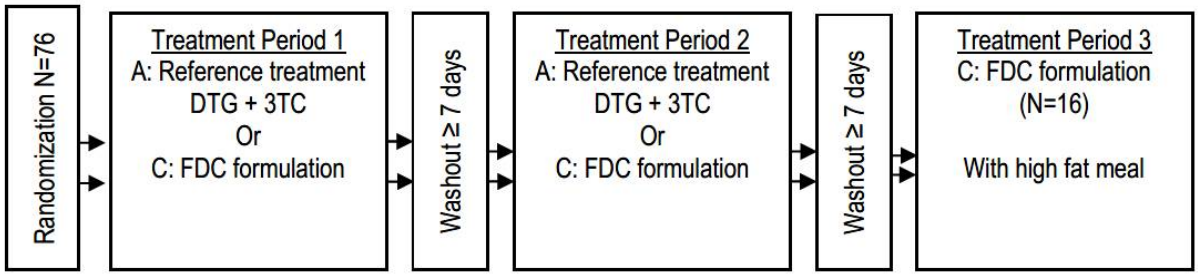
2.3. Study Design

Overview of Study Design and Key Features

Part 1, Bioequivalence and Food Effect with Monolayer FDC Tablet



Part 2, Bioequivalence and Food Effect with Bilayer FDC Tablet



Design Features	In both Part 1 and Part 2 (if conducted), the first two treatment periods will be randomized, open-label, 2-period, single-dose, crossover. In each study part, the first 16 subjects who complete the first two treatment periods, and consent to continue, will return for a third treatment period and receive a single dose of the FDC tablet formulation (monolayer in Part 1, bilayer in Part 2) administered with a high fat meal.
Dosing	• In the first two treatment periods (BE), each subject will be randomized to either receive an oral reference treatment DTG (50 mg) plus EPIVIR(300 mg); or an oral FDC (DTG 50mg/3TC 300mg) formulation (monolayer in Part 1, bilayer in Part 2) in two periods per the two sequences specified below under fasted state. • The first 16 subjects who complete the first two treatment periods in each part, and consent to continue, will return for a third treatment period and receive an oral FDC (DTG 50mg/3TC 300mg) formulation (monolayer in Part 1, bilayer in Part 2) administered with a high fat meal. • Total duration for each subject (from screening to follow-up) will be a minimum of 5 weeks, with a maximum of up to 9 weeks, depending on the screening period and whether a subject participates the third period.

<table>
<tr><th colspan="2">Overview of Study Design and Key Features</th></tr>
<tr><td>Treatment Assignment</td><td>Subjects will be randomized to one of the following two sequences in Part 1 and Part 2, if conducted.
<table>
<tr><th>Sequences</th><th>Period 1</th><th>Period 2</th><th>Period 3</th></tr>
<tr><td></td><td colspan="2">Bioequivalence, 2 Period-Crossover Design</td><td>Food effect[a]</td></tr>
<tr><td colspan="4">Part 1</td></tr>
<tr><td>A/B, n=38</td><td>A</td><td>B</td><td rowspan="2">B Fed (n=16)</td></tr>
<tr><td>B/A, n=38</td><td>B</td><td>A</td></tr>
<tr><td colspan="4">Part 2 (if conducted)</td></tr>
<tr><td>A/C, n=38</td><td>A</td><td>C</td><td rowspan="2">C Fed (n=16)</td></tr>
<tr><td>C/A, n=38</td><td>C</td><td>A</td></tr>
</table>
Treatment A = DTG 50 mg tablet (clinical image) plus a single EPIVIR 300 mg tablet
Treatment B = DTG 50 mg/3TC 300 mg FDC monolayer formulation (Product code AH)
Treatment C = DTG 50 mg/3TC 300 mg FDC bilayer formulation (Product code TBD)
a. first 16 subjects who complete the two treatment periods, and consent to continue to complete period 3 in each part

Subjects will be administered the 1st treatment in the sequence in the 1st period; the 2nd treatment in the sequence in the 2nd period;

• Each treatment will be administered in the fasted state after at least 10 hours of fasting in the first two treatment periods.
• Each treatment will be administered with a high fat meal in the third treatment period.</td></tr>
<tr><td>Interim Analysis</td><td>Following completion of Part 1, preliminary PK data from Part 1 will be analyzed. The point estimates and corresponding 90% CIs will be constructed for the ratio of the geometric mean of the test treatment (monolayer) to the geometric mean of the reference treatments, μ(test)/μ(reference) for $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, and C_{max} for both DTG and 3TC.
A similar preliminary PK analysis as was conducted following Part 1, will also be performed for Part 2.The result will be used for planning a future Phase III study. An independent statistics and programming team will perform the preliminary PK analyses for both parts.</td></tr>
</table>

2.4. Statistical Hypotheses

The first two treatment periods of each part of this study are designed to test the bioequivalence of FDC tablets of DTG and 3TC (test treatment) relative to co-administered DTG plus 3TC (reference treatment) all under fasting condition. The null hypothesis is that the true ratio of the geometric mean of the test treatment to the geometric mean of the reference treatment, μ(test)/μ(reference), for each primary PK endpoint, is either less than 0.800 or greater than 1.250. The alternate hypothesis is that the true ratio of the test treatment geometric mean to the reference treatment geometric mean is greater than or equal to 0.800 and less than or equal to 1.250. Symbolically, this

is expressed as follows:

- H(0): μ(test)/μ(reference) < 0.800 or μ(test)/μ(reference) > 1.250, i.e., treatments are not bioequivalent versus
- H(1): 0.800 ≤ μ(test)/μ(reference) ≤ 1.250 i.e., treatments are bioequivalent.

For each PK parameter designated as a primary endpoint (see Section 2.2), a two one-sided t-test (TOST) procedure (Schiurmann, 1987) with α=0.05 for each one-sided test will be used to test this set of hypotheses. This is equivalent to requiring that a 90% interval for the true ratio of test to reference geometric means falls entirely within the range of 0.800 to 1.250. To declare bioequivalence of FDC tablet DTG and 3TC to co-administered DTG plus 3TC, the primary PK endpoints for both analytes should demonstrate bioequivalence.

For the food effect portion(s), no formal hypothesis will be tested and an estimation approach will be used to evaluate the effect of food on the FDC tablet.

3. PLANNED ANALYSIS

3.1. Interim Analyses

Following completion of Part 1, preliminary PK data from Part 1 will be analyzed. The point estimates and corresponding 90% CIs will be constructed for the ratio of the geometric mean of the test treatment (monolayer) to the geometric mean of the reference treatments, μ(test)/μ(reference) for $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, and C_{max} for both DTG and 3TC.

A similar preliminary PK analysis as was conducted following Part 1, will also be performed for Part 2. This is simply bringing forward a part of the planned end of study analysis to pre-DBF, but after all subjects have completed the trial, in order to expedite decision making. The PK parameter data for the preliminary analysis will be based on the nominal sampling times.

The result will be used for planning a future Phase III study. An independent statistics and programming team will perform the preliminary PK analyses for both part1. As the PK data are analyzed separately for each part of the study, there will be no adjustments for multiplicity.

3.2. Final Analyses

Analysis	Details
Final Analyses	Final analyses will be performed after the completion of the study and final database authorization.

The final planned analyses will be performed after the completion of the following sequential steps:

1. All subjects have completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and final database release and database freeze has been declared by Data Management.

3. All criteria for unblinding the randomisation codes have been met.
4. Randomisation codes have been distributed according to RandAll NG procedures.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screening Population	All subjects who signed the consent form will be included in this population.	• Subject Disposition
Safety Population	All subjects who enrolled in the study and received at least one dose of study drug will be included in the Safety Population.	• Study Population • Safety
Pharmacokinetic (PK) Plasma Concentration	The PK Plasma Concentration Population will include all subjects who undergo plasma PK sampling and have evaluable PK assay results for DTG or 3TC.	• PK concentration listings, • calculating PK parameters, • PK parameter listings • plotting of the individual concentration-time profiles
Pharmacokinetic (PK) Parameter BE Summary	The PK Parameter BE Summary Population will include all subjects who have evaluable PK parameters for both analytes and for both Period 1 and Period 2. Data from subjects who vomit within 4 hours of study drug administration will not be considered as evaluable.	• PK concentration summary • PK parameter summary and figure • Statistical analysis of parameter data • Excluded subjects will be included in footnotes for summary tables
Pharmacokinetic (PK) Parameter FD Summary	The PK Parameter FD Summary Population will include subjects who participate in the food effect part of study, and have evaluable PK parameters for both fed and fasted administration of the FDC tablet formulation. Data from subjects who vomit within 4 hours of study drug administration will not be considered as evaluable.	• PK concentration summary • PK parameter summary and figure • Statistical analysis of parameter data • Excluded subjects will be included in footnotes for summary tables

NOTES :

- Please refer to Appendix 11 which details the population to be used for each display being generated.
- Additional PK concentration and parameter summary tables will be provided by using the PK plasma concentration population if there are subjects with only 1 period PK data or subjects who vomit.

4.1. Protocol Deviations

- All protocol deviations will be listed with flags to indicate whether a PD is important and results in exclusion from the analysis population.
- Important deviations will also be summarized, reported in the study report (Please refer to Appendix 1: Protocol Deviation Management).
- Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.
    - Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorised in the protocol deviations dataset.
    - This dataset will be the basis for the listings of protocol deviations.
- A separate listing of all inclusion/exclusion criteria deviations will also be provided.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

Table 1 provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions.

Table 1 Overview of Appendices

Section	Component
10.1	Appendix 1: Protocol Deviation Management
10.2	Appendix 2: Data Management
10.3	Appendix 3: Time & Events
10.4	Appendix 4: Treatment States and Phases
10.5	Appendix 5: Data Display Standards & Handling Conventions
10.6	Appendix 6: Derived and Transformed Data
10.7	Appendix 7: Premature Withdrawals & Handling of Missing Data
10.8	Appendix 8: Values of Potential Clinical Importance
10.9	Appendix 9: Model Checking and Diagnostics for Statistical Analyses.
10.10	Appendix 10: Abbreviations and Trade Marks
10.11	Appendix 11: List of Data Displays
10.12	Appendix 12: Example Mock Shells for Data Displays

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

The study population analyses will be based on the "Safety" population, unless otherwise specified.

Table 2 provides an overview of the planned study population analyses, with full details of data displays being presented in Appendix 11: List of Data Displays.

Table 2 Overview of Planned Study Population Analyses

Display Type	Data Displays Generated		
	Figure	Table	Listing
Randomization			
Randomization			Y
Subject Disposition			
Subject Disposition		Y	
Reasons for Screening Failures			Y[1]
Reasons for Withdrawals			Y
Important[3] Protocol Deviations		Y	Y
Inclusion and Exclusion Criteria Deviations			Y
Subjects Excluded from Analysis Populations			Y[2]
Demography			
Demographics Characteristics		Y	Y
Race & Racial Combinations		Y	Y
Concomitant Medications			
Concomitant Medication			Y

NOTES:
- Y = Yes display generated.

1. Conditional displays, if data is available listing will be generated.
2. Listing of subjects excluded from any population will be generated only.
3. All protocol deviations will be listed, with important protocol deviations summarized.

7. PRIMARY STATISTICAL ANALYSES

7.1. Pharmacokinetic Analyses

The reconciliation of the PK Case Report Form (CRF) and SMS2000 data will be performed by, or under the direct auspices of, Clinical Pharmacology Sciences and Study Operations (CPSSO) data management, GlaxoSmithKline.

The merge of PK concentration data, randomization and CRF data will be performed by Study Data Tabulation Model (SDTM) programmer at Quintiles and the analysis PK

concentration dataset and WinNonLin files will be created by statistics and programming, PAREXEL, under the direct auspices of statistics and programming, Quantitative Sciences (QSci), GlaxoSmithKline.

Derivation of pharmacokinetic parameters will be performed by Clinical Pharmacology Modelling & Simulation (CPMS), QSci, GlaxoSmithKline.

Statistical Analysis of pharmacokinetic parameters will be performed by statistics and programming, PAREXEL, under the direct auspices of statistics and programming, QSci, GlaxoSmithKline.

7.1.1. Overview of Planned Pharmacokinetic Analyses

The pharmacokinetic (PK) analyses will be based on the "PK Plasma Concentration" or "PK Parameter BE or FD Summary' populations, unless otherwise specified.

Table 3 provides an overview of the planned analyses, with full details being presented in Appendix 11: List of Data Displays.

Table 3 Overview of Planned Pharmacokinetic Analyses

Endpoints	Untransformed				Log_e-Transformed			
	Summary		Individual		Summary		Individual	
	F	T	F	L	F	T	F	L
Plasma Drug Concentrations	Y [1] [2]	Y	Y [1]	Y				
Derived PK Parameters		Y	Y[3]	Y	Y[4]	Y	Y	
Statistical Analysis PK Parameters					Y[5]	Y		Y[6]

NOTES :

- T = Table, F = Figures, L = Listings, Y = Yes display generated.
- Summary = Represents TFL related to any summaries (descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- T_{max} and t_{lag} are not log transformed.

1. Linear and Semi-Log plots will be created on the same display.
2. Mean (+SD) and Median plots will be generated.
3. Comparative Plot of Individual DTG and 3TC Plasma PK Parameter versus treatments
4. Treatment Comparative Plot of adjusted geometric mean (95% CI) with Individual Subject Plasma PK Parameters will be generated.
5. Geometric Mean Treatment Ratio and 90% CI of DTG and 3TC Plasma PK Parameters will be generated.
6. Supportive SAS Output from Statistical Analysis of Log_e-transformed DTG and 3TC Plasma PK Parameters

7.1.2. Drug Concentration Measures

Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 10.5.3 Reporting Process & Standards).

7.1.3. Pharmacokinetic Parameters

7.1.3.1. Deriving Pharmacokinetic Parameters

- PK analyses will be the responsibility of the CPMS department within GSK or their designee. Plasma DTG and 3TC concentration-time data will be analyzed by non-compartmental methods according to current working practices and using Phoenix WinNonlin 6.3 or higher. Calculations will be based on the actual sampling times recorded during the study and based on nominal sampling times. From the plasma concentration-time data, the following PK parameters will be determined, as data permit: C_{max}, T_{max}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, $AUC_{(0-24)}$, $t_{1/2}$, t_{lag}, C_{24}, C_t, λz, $\%AUC_{ex}$, Vz/F, t and CL/F.
- Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 10.5.3 Reporting Process & Standards).
- Non-compartmental analysis will be performed in accordance with GSK PK Guidance document GUI_51487.
- Two sets of PK parameters will be derived for each subject, analyte and treatment: one set based on actual sampling times and one set based on nominal times.
- Pharmacokinetic parameters described in Table 4 will be determined from plasma concentration-time data, as data permit.

Refer Appendix 7 Section 10.7.2.2 for handling of PK Concentration data.

Table 4 Derived Pharmacokinetic Parameters

Parameter	Parameter Description
$AUC_{(0-\infty)}$	Area under the concentration-time curve from time zero extrapolated to infinity
$AUC_{(0-t)}$	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C_t) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
$AUC_t(\%)$	Percent of the area measured by $AUC_{(0-t)}$ relative to the extrapolated $AUC_{(0-\infty)}$
$AUC_{(0-24)}$	Area under the plasma concentration time curve from time zero to 24 hours
$\%AUC_{ex}$	% of $AUC_{(0-\infty)}$ that was extrapolated
C_{24}	Drug concentration at 24 hours post-dose
C_{max}	Maximum observed concentration, determined directly from the concentration-time data.
C_t	last quantifiable concentration
t	time of last quantifiable concentration
T_{max}	Time to reach C_{max}, determined directly from the concentration-time data.
tlag	Lag time before observation of drug concentrations in sampled matrix

Parameter	Parameter Description
λz	Apparent elimination rate constant
$t_{½}$	Apparent terminal half-life will be calculated as: $t_{½}$ = ln2 / Lambda_z (NOTE: Lambda_z is the terminal phase rate constant).
CL/F	The apparent oral clearance (CL/F) will be calculated as CL/F = Dose/$AUC_{(0-\infty)}$
Vz/F	Apparent oral volume of distribution

7.1.3.2. Statistical Analysis of Pharmacokinetic Parameters

Two sets of bioequivalence assessments and food effect will be performed based on:

- PK parameters derived based on actual sampling times
- PK parameters derived based on nominal sampling times

For each of the parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, C_t, CL/F and $t_{1/2}$, the following summary statistics will be calculated and tabulated by treatment (dose):

- **Untransformed Data :** N, n, arithmetic mean, %CV, 95% confidence interval (CI) for the arithmetic mean, SD, median, minimum, and maximum.
- **Log_e-transformed Data:** Geometric mean, 95% CI for the geometric mean, SD of log_e-transformed data and %CVb

For $\%AUC_{ex}$, T_{max}, t_{lag}, λz, t, and Vz/F, the summary statistics specified for untransformed data above will be generated.

PK data will be listed and may be presented in graphical form and will be summarized descriptively. All PK data will be stored in the Archives, GlaxoSmithKline R& D.

Statistical analyses of the PK parameter data will be the responsibility of Clinical Statistics, GlaxoSmithKline or their designee.

The PK parameters for DTG and 3TC (except T_{max} and t_{lag}) will be log_e-transformed and separately analyzed using a mixed effects model. For the analysis of bioequivalence, the model will include fixed effect terms for period and treatment. Subject will be treated as a random effect in the model. For the analysis of food effect, the model will include a fixed effect term for treatment (fed versus fasted) and a random effect term for subject. Point estimates and their associated 90% CIs will be constructed for the differences in PK parameter values between test and reference treatments for the treatment comparisons. The point estimates and their associated 90% CIs will then be back-transformed to provide point estimates and 90% CIs for the ratios of PK parameters between test and reference treatments.

T_{max} and t_{lag} of DTG and 3TC will be separately analyzed with the non-parametric Wilcoxon matched pair method to compute point estimates and associated 90% confidence intervals for the median differences between test and reference treatments.

Primary and Secondary Comparisons of Interest

	DTG or 3TC PK Parameter	Test	Reference	Assessment
Primary	$AUC_{(0-\infty)}$, $AUC_{(0-t)}$, C_{max},	Treatment B	Treatment A	Bioequivalence
		Treatment C (if Part 2 is conducted)	Treatment A	
Secondary	CL/F, $AUC_{(0-24)}$, C_{24}, $t_{1/2}$	Treatment B	Treatment A	Bioequivalence
		Treatment C (if Part 2 is conducted)	Treatment A	
	$AUC_{(0-\infty)}$, $AUC_{(0-t)}$, C_{max}, CL/F, $AUC_{(0-24)}$, C_{24}, $t_{1/2}$	Treatment B Fed	Treatment B Fasted	Food Effect
		Treatment C Fed (if Part 2 is conducted)	Treatment C Fasted	

Estimates of within-subject variability for $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, C_{max}, CL/F, $AUC_{(0-24)}$, C_{24}, $t_{1/2}$ will also be provided, where CVw(%) = SQRT(exp(MSE) – 1)×100 and MSE is the residual mean squared error from the model. CV_w represents a pooled measure of within-subject variability across the treatments A and B or A and C (if Part 2 is conducted).

Comparative Plot of Individual subject DTG and 3TC Plasma PK Parameter Versus Treatment will be generated.

Treatment Comparative Plots of adjusted geometric mean (95% CI) with Individual Subject Plasma PK Parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, C_{max}, CL/F, $AUC_{(0-24)}$, C_{24}, $t_{1/2}$ will be generated.

Plots will also be provided showing the adjusted geometric mean ratio of test to reference treatment for $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, C_{max}, CL/F, $AUC_{(0-24)}$, C_{24}, $t_{1/2}$ with 90% CIs.

The SAS output from the statistical models and the assessment of assumptions underlying the models will be included in a listing of supportive SAS output.

Additional PK displays for Canada specific submission requirements will also be provided.

8. SECONDARY STATISTICAL ANALYSES

8.1. Safety Analyses

The safety analyses will be based on the “Safety” population, unless otherwise specified.

8.1.1. Overview of Planned Analyses

Table 5 provides an overview of the planned analyses, with full details of data displays being presented in Appendix 11: List of Data Displays.

Table 5 Overview of Planned Safety Analyses

Endpoint	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Exposure								
Exposure				Y				
Adverse Events								
All AE's	Y			Y				
Serious AE's	Y			Y				
Drug Related AEs	Y			Y				
Withdrawal AE's	Y			Y				
Relationship Between System Organ Class And Verbatim Text				Y				
Subject Numbers for Individual AEs				Y				
Laboratory Values								
Clinical Chemistry	Y				Y			
Hematology	Y				Y			
Abnormal Clinical Chemistry				Y				
Abnormal Hematology				Y				
Abnormal Urinalysis				Y				
ECG's								
ECG Findings	Y							
ECG Values	Y							
ECG Values Outside the PCI Range				Y				
All ECG Values for Subjects with a Value of PCI				Y				
Abnormal ECG Findings				Y				
Vital Signs								
Vitals Values	Y				Y			
Vital Signs Measurements Outside the PCI Range				Y	Y			
All Vital Signs for Subjects with Values of PCI				Y				

NOTES :

- T = Table, F = Figures, L = Listings, Y = Yes display generated.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

9. REFERENCES

GlaxoSmithKline Document Number 2016N286215_00: An Open-label, Randomized, Single dose, Crossover, Pivotal Bioequivalence Study of Fixed-dose Combination Tablets of Dolutegravir and Lamivudine versus Dolutegravir and Lamivudine single entities and Food Effect Assessment in Healthy Volunteers. Effective Date: 12-JAN-2017

GlaxoSmithKline Document Number 2016N286215_01: An Open-label, Randomized, Single dose, Crossover, Pivotal Bioequivalence Study of Fixed-dose Combination Tablet(s) of Dolutegravir and Lamivudine versus Dolutegravir and Lamivudine single entities and Food Effect Assessment in Healthy Volunteers Effective Date: 07-FEB-2107

Schiurmann DJ. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. *J Pharmacokinetics Biopharm* 1987; 15:657-679.

10. APPENDICES

Section	Appendix
RAP Section 4: Analysis Populations	
Section 10.1	Appendix 1: Protocol Deviation Management
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
Section 10.2	Appendix 2: Data Management
Section 10.3	Appendix 3: Time and Events
Section 10.4	Appendix 4: Treatment States & Phases
Section 10.5	Appendix 5: Data Display Standards & Handling Conventions • Study Treatment & Sub-group Display Descriptors • Baseline Definitions & Derivations • Reporting Process & Standards
Section 10.6	Appendix 6: Derived and Transformed Data • General • Study Population • Safety • Pharmacokinetic
Section 10.7	Appendix 7: Premature Withdrawals & Handling of Missing Data • General • Study Population & Safety
Section 10.8	Appendix 8: Values of Potential Clinical Importance • Laboratory Values • ECG • Vital Signs
Section 10.9	Appendix 9: Model Checking and Diagnostics for Statistical Analyses
Other RAP Appendices	
Section 10.10	Appendix 10: Abbreviations & Trade Marks
Section 10.11	Appendix 11: List of Data Displays
Section 10.12	Appendix 12: Example Mock Shells for Data Displays

10.1. Appendix 1: Protocol Deviation Management

A subject meeting any of the following criteria will be excluded from the PK Parameter BE and/or FD Summary Population:

Number	Exclusion Description
01	Failure of any inclusion/exclusion criteria, but subject is still enrolled
02	A subject with emesis occurring within 4 hours of the dose

10.2. Appendix 2: Data Management

Data Type	Source	Format of Data	Planned Date of Final File[1]	Responsibility
Safety	Database	SDTM	DBF	CPSSO
PK Concentration	SMS2000 data files	dat file	DBF	BIB/BESM
PK Concentration (ADPC), WNL File	PK concentration data (SDTM PC), exposure (EX) and demography (DM) datasets[2]	ADaM, CSV file	DBF + 5 Days[1]	QSci
PK Parameters	WNL file	CSV file	PK Concentration, WNL file + 5 Days	CPMS

1. Provided SDTM PC, EX and DM are in time and clean
2. PK concentration data is released via SMS2000 by Bioanalysis, Immunogenicity and Biomarkers (BIB)/Bioanalytical External Study Monitors (BESM) and the SDTM PC contains date/times and PK sample ID

10.3. Appendix 3: Time & Events

Screening Assessments

Visit Window (relative to Day 1)	Day -30 to -2	Notes
Informed Consent	X	
Demographics	X	
Physical examination height, weight and BMI	X	
Medical/medication/ history	X	*Medical/medication/drug and alcohol history will be recorded at screening, and updated at admission.*
Urine drug / Cotinine and Breathalyzer screening	X	
12-lead ECG and Vital Signs	X	
Serum or urine hCG test (female subjects only)	X	• *See inclusion Protocol criterion #6.* • *Performed at site standard procedure.*
FSH and estradiol (women)	X	
HIV, Hep B and Hep C Screen	X	
Hematology/Chemistry/Urinalysis tests	X	

Treatment Period Assessments

Assessments	All Dosing Periods							Follow-up	*Notes* *Day -1 of Periods 2 to 3 may be the same day as Day 6 of prior periods*
	Day -1	Day 1			Day 2	Day 3	Day 4		
		Pre-dose	0 hr	Post Dose	-	48 hr	72 hr		
Admission to Unit	X								
Discharge						X			
Outpatient Visit							X	X	*Follow-up visit will occur 7 to 14 days post last dose.*
12-lead ECG	X								*Single ECGs will be collected at Screening and on Day-1 of Period 1 only. Additional ECGs may be performed at the discretion of the investigator.*
Vital signs	X	X		At 4 hours post-dose	X	X	X	X	*Single measurements performed at all time points.*
Brief Physical Exam	X								• *Brief examinations may be made full examinations and laboratory procedures may be repeated, if needed, at the discretion of the Investigator.* • *Illicit Drug/Alcohol/Cotinine/pregnancy screening will be performed in accordance with the sites' standard practice.* • *Clinical laboratory tests – see Protocol Table 5.*
Urine Drug/ Cotinine and Breathalyzer	X								
Pregnancy test	X							X	
Clinical laboratory tests	X							X	
Dosing			**X**						*Subject will be dosed while in the seated position.*
Pharmacokinetic Sampling		X		Collect at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, and 48 hours post-dose			X		*Pre-dose (within 15 minutes prior to dosing).* *4 hour post dose sample must be taken prior to provision of food.* *Permitted window for the collection of PK sample at each time point will be specified in BioPacket.*
Meals – (Treatment periods 1 and 2)	Fasted from 10 hours prior to dosing to 4 hours post-dose			Standard for the study center					*See also Protocol Section 6.10.1.1*
Meals - Treatment Period 3 (Fed Conditions only)	*Fasted from 10 hours prior to test meal and dosing then through 4 hours post-dose*			*Standard for the study center*					*Entire meal to be consumed in 25 minutes or less and dosing will be administered 30 minutes after the start of the meal. See also Protocol Section 6.10.1.2*
Adverse Events	X	←==========X==========→						X	
Concomitant medications	X	←==========X==========→						X	

10.4. Appendix 4: Treatment States and Phases

10.4.1. Treatment Phases

Assessments and events will be classified according to the time of occurrence relative to the start and/or stop date/time of the study treatment.

Treatment Phase	Definition
Pre-Treatment	Date/Time ≤ Study Treatment Start Date/Time
On-Treatment	Study Treatment Start Date/Time < Date/Time ≤ [Study Treatment Stop Date/Time + 3 Days]
Post-Treatment	Date/Time > [Study Treatment Stop Date/Time + 3 Days]

10.4.2. Treatment States

Assessments and events will be classified according to time of occurrence relative to the start and/or stop date/time of the study treatment.

10.4.2.1. Treatment States for AE Data

Treatment State	Definition
Pre-Treatment	AE Start Date/Time < Study Treatment Start Date/Time
On-Treatment	If AE onset date/time is on or after treatment start date/time & 3 or fewer days after the treatment stop date/time Study Treatment Start Date/Time ≤ AE Start Date/Time ≤ [Study Treatment Stop Date/Time + 3]
Post-Treatment	If AE onset date/time is more than 3 days after the treatment stop date/time AE Start Date/Time > [Study Treatment Stop Date/Time + 3]
Onset Time Since First Dose (Days)	If Treatment Start Date/Time > AE Onset Date/Time = AE Onset Date - Treatment Start Date If Treatment Start Date/Time ≤ AE Onset Date/Time = AE Onset Date - Treatment Start Date +1 Missing otherwise
Duration (Days)	AE Resolution Date – AE Onset Date + 1
Drug-related	If relationship is marked 'YES' on eCRF

NOTES:

- If the study treatment stop date is missing then the AE will be considered to be On-Treatment.

10.5. Appendix 5: Data Display Standards & Handling Conventions

10.5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions		
RandAll NG		Data Displays for Reporting
Code	Description	Description
A	DTG 50mg plus EPIVIR 300mg	A
B	DTG 50mg and 3TC 300mg FDC monolayer	B
C	DTG 50mg and 3TC 300mg FDC bilayer	C
B_Fed[1]	DTG 50mg and 3TC 300mg FDC monolayer fed	B_Fed
C_Fed[1]	DTG 50mg and 3TC 300mg FDC bilayer fed	C_Fed

[1] Treatments B_Fed and C_Fed are assigned.
NOTES: Add the following footnote for treatment description.
A: DTG 50mg plus EPIVIR 300mg
B: DTG 50mg and 3TC 300mg FDC monolayer
C: DTG 50mg and 3TC 300mg FDC bilayer
B_Fed: DTG 50mg and 3TC 300mg FDC monolayer fed
C_Fed: DTG 50mg and 3TC 300mg FDC bilayer fed

10.5.2. Baseline Definition & Derivations

10.5.2.1. Baseline Definitions

For all endpoints (except as noted in the table) the baseline value will be the latest pre-dose assessment.

Table 6 Baseline Definitions

Parameter	Study Assessments Considered As Baseline			Baseline Used in Data Display
	Screening	Day -1	Day 1 (Pre-Dose)	
Safety				
Lab	X	X		Day -1
Vital Signs (blood pressure, and pulse rate)	X	X	X	Day 1 (Pre-Dose) for each Period

10.5.2.2. Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit Value – Baseline

NOTES :

- Unless otherwise specified, the baseline definitions specified in Section 10.5.2.1 Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.
- The baseline definition will be footnoted on all change from baseline displays.

10.5.3. Reporting Process & Standards

Reporting Process	
Software	
• The currently supported versions of SAS and S-Plus software will be used.	
Reporting Area	
HARP Server	: US1SALX00259-HARP PROD-US
HARP Area	: \ARPROD\GSK1349572\mid204994\Final
QC Spreadsheet	: \ARWORK\GSK1349572\mid204994\Final\Documents
Analysis Datasets	
• Analysis datasets will be created according to Clinical Data Interchange Standards Consortium (CDISC) standards (SDTM IG Version 3.1.3 & Analysis Data Model (ADaM) Implementation Guide (ADaM IG) Version 1.0 or higher dataset standards)	
Generation of Rich Text Format (RTF) Files	
• RTF files will be generated for summary displays.	

Reporting Standards
General
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: o 4.03 to 4.23: General Principles o 5.01 to 5.08: Principles Related to Data Listings o 6.01 to 6.11: Principles Related to Summary Tables o 7.01 to 7.13: Principles Related to Graphics
Formats
• All data will be reported according to the actual treatment the subject received unless otherwise stated. • GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected. • Numeric data will be reported at the precision collected on the eCRF.

Reporting Standards	
• The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.	
Planned and Actual Time	
• Reporting for tables, figures and formal statistical analyses : o Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated. o The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate. • Reporting for Data Listings: o Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1). o Unscheduled or unplanned readings will be presented within the subject's listings. o Visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings but omitted from figures, summaries and statistical analyses.	
Unscheduled Visits	
• Unscheduled visits will not be included in summary tables. • Unscheduled visits will not be included in figures. • All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Reporting of Pharmacokinetic Concentration Data	
Descriptive Summary Statistics	Refer to IDSL Statistical Principle 6.06.1 Assign zero to NQ values (Refer to GUI_51487 for further details)
Reporting of Pharmacokinetic Parameters	
Descriptive Summary Statistics. (Un-Transformed)	N, n, arithmetic mean, 95% confidence interval (CI) for the arithmetic mean, SD, median, minimum, maximum and CV(%) • CV(%)=(SD/mean)*100
Descriptive Summary Statistics. (Log_e Transformed)	N, n, geometric mean, 95% CI of geometric mean, standard deviation (SD) of logged data and between-subject geometric coefficient of variation (CV_b (%)) will be reported. • Geometric mean = exp (mean on log_e scale) • CV_b (%) = $\sqrt{}$ (exp(SD^2) - 1) * 100 [NOTE: SD = SD of log_e transformed data]
Parameters Not Being Log_e Transformed	$\%AUC_{ex}$, T_{max}, t_{lag}, t, λz, Vz/F
Listings	Include PK Parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, $\%AUC_{ex}$, C_{max}, C_{24}, C_t, t, T_{max}, λz, $t_{1/2}$, t_{lag}, CL/F, Vz/F, ratios (test:

Reporting Standards	
	reference) for $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{24} and C_{max}; and the ratio of $AUC_{(0-t)}/AUC_{(0-\infty)}$ (AUC_t(%)) for Canada specific submission requirement.
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

10.6. Appendix 6: Derived and Transformed Data

10.6.1. General

Multiple Measurements at One Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • If there are two values within a time window the value closest to the target day for that window will be used. If values are the same distance from the target then the mean will be taken.
Study Day

• Calculated as the number of days from Treatment start date :
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < Treatment start Date → Study Day = Ref Date – Treatment start Date
  • Ref Data ≥ Treatment start Date → Study Day = (Ref Date – Treatment start Date) + 1

10.6.2. Study Population

Demographics
Age
• GSK standard IDSL algorithms will be used for calculating age using date of the screening visit relative to birth date, where birth date is imputed as: • Any subject with a missing date and month will have this imputed as '30th June'. • Birth date will be presented in listings as 'YYYY'.
Body Mass Index (BMI)
• Calculated as **Weight (kg) / [Height (m)]^2**

10.6.3. Safety

ECG Parameters
RR Interval
• IF RR interval (msec) is not provided directly, then RR can be derived as : [1] If QTcB is machine read & QTcF is not provided, then : RR = [(QT/QTcB)^(2)]*1000 [2] If QTcF is machine read and QTcB is not provided, then: RR = [(QT/QTcF)^(3)]*1000
Corrected QT Intervals
• When not entered directly in the eCRF, corrected QT intervals using Bazett's (QTcB) and Fredericia's (QTcF) formulas will be calculated, in msec, depending on the availability of other measurements. • IF RR interval (msec) is provided then missing QTcB and/or QTcF will be derived as : $QTcB = \frac{QT}{\sqrt{\frac{RR}{1000}}}$ $QTcF = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$

Laboratory Parameters
• If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value. • Example 1: 2 Significant Digits = '< x ' becomes x – 0.01 • Example 2: 1 Significant Digit = '> x' becomes x + 0.1 • Example 3: 0 Significant Digits = '< x' becomes x – 1

10.7. Appendix 7: Premature Withdrawals & Handling of Missing Data

10.7.1. Premature Withdrawals

Element	Reporting Detail
General	• All subjects who withdraw prematurely from the study/study drug will be documented and the reason for their withdrawal recorded in the final Clinical Pharmacology Study Report (CPSR). • All available data collected up until the point of withdrawal, and the follow-up visits will be used in the analyses and will be listed and all available planned data will be included in the summaries according to the populations defined in Section 4. • Any data collected up until the point of withdrawal, and the follow-up visits will be used in the analyses. • In the event that the study is prematurely discontinued, all available data will be listed and a review carried out by the study team to assess which statistical analyses are still considered appropriate.

10.7.2. Handling of Missing Data

Element	Reporting Detail
Outliers	• Any subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

10.7.2.1. Handling of Missing Dates

Element	Reporting Detail
General	Partial dates will be displayed as captured in subject listing displays.

10.7.2.2. Handling of PK Concentration Data

Element	Reporting Detail
General	• The PK Plasma Concentration Population will include all subjects who undergo plasma PK sampling and have evaluable PK assay results for DTG or 3TC. • Data from subjects who vomit within 4 hours of study drug administration or who have major protocol deviations will be excluded from PK concentration summary, PK parameter summary and statistical comparisons but will be included in the Listing and flagged. • This population will be used for listing PK concentrations, parameters, calculating PK parameters and plotting of individual concentration-time files. • If the pre-dose concentration is ≤ 5% of Cmax value in a subject, the concentration data for that subject without any adjustments will be included in PK and statistical analysis. If the pre-dose concentration is > 5% of Cmax value in a subject, then the concentration data for that subject will not be included in PK and statistical analysis and only the concentration data of that subject(s) will be presented • If during clinical phase, 3 consecutive samples in any phase i.e. (Absorption, Distribution and Metabolism / Excretion) are found to be missing then data for that subject will not be included in PK and statistical analysis and only the concentration data of that subject(s) will be presented

10.8. Appendix 8: Values of Potential Clinical Importance

10.8.1. Laboratory Values

Division of AIDS (DAIDS, Version 2.0, November 2014) AE grade 2 and above of lab abnormalities will be listed by subject, period/treatment, visit, and actual date and time.

10.8.2. ECG

ECG Values of Potential Clinical Importance (Healthy Volunteers)

ECG Parameter	Potential Clinical Importance Range (PCI)	Unit
Absolute QTc Interval	>450	msec
PR Interval	<110 and >220	msec
QRS Interval	<75 and >110	msec

10.8.3. Vital Signs

Vital Signs Values of Potential Clinical Importance (Healthy Volunteers)

VS Parameter	Potential Clinical Importance Range (PCI)	Unit
Systolic Blood Pressure	<85 and >160	mmHg
Diastolic Blood Pressure	<45 and >100	mmHg
Heart Rate	<40 and >110	bpm

Vital Signs change from Baseline Flagging Range

VS Parameter	Flagging Criteria	Unit
Systolic Blood Pressure (Change from Baseline)	Increase ≥20	mmHg
	Increase ≥40	
	Decrease ≥ 20	
	Decrease≥40	
Diastolic Blood Pressure (Change from Baseline)	Increase ≥ 10	mmHg
	Increase≥20	
	Decrease ≥ 10	
	Decrease≥20	
Heart Rate (Change from Baseline)	Increase ≥ 15	bpm
	Increase ≥ 30	
	Decrease ≥ 15	
	Decrease ≥ 30	

10.9. Appendix 9: Model Checking and Diagnostics for Statistical Analyses

10.9.1. Statistical Analysis Assumptions

Endpoint(s)	• AUC(0-∞), AUC(0-t), Cmax, CL/F, AUC(0-24), C24, t1/2
Analysis	• Linear Mixed Model

Assumptions:

- For the Linear Mixed Model, model assumptions will be applied, but appropriate adjustments may be applied based on the data.
- The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.
- An unstructured covariance structure for the G matrix will be used by specifying 'type=UN' on the RANDOM line.
    - In the event that this model fails to converge, alternative covariance structures may be considered such as VC or CS.
    - Akaike's Information Criteria (AIC) will be used to assist with the selection of covariance structure.
- Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.
- Sensitivity analysis will be performed if the normality assumptions are violated due to presence of outliers.

10.10. Appendix 10 - Abbreviations & Trade Marks

10.10.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
ADaM IG	Analysis Data Model Implementation Guide
AE	Adverse Event
AUC	Area under concentration-time curve
$AUC_{(0-\infty)}$	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
$AUC_{(0-t)}$	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration
$AUC_{(0-24)}$	Area under the plasma concentration time curve from time zero to 24 hours
$\%AUC_{ex}$	% of AUC(0-∞) that was extrapolated
$AUC_t(\%)$	Percent of the area measured by AUC(0-t) relative to the extrapolated AUC(0-∞)
BE	Bioequivalence
BESM	Bioanalytical External Study Monitors
BIB	Bioanalysis, Immunogenicity and Biomarkers
C_{24}	Drug concentration at 24 hours post-dose
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CL/F	The apparent oral clearance
C_{max}	Maximum observed concentration
CP	Clinical Programming
CPMS	Clinical Pharmacology Modelling & Simulation
CPSSO	Clinical Pharmacology Sciences and Study Operations
CRF	Case record form
CS	Clinical Statistics
C_t	last quantifiable concentration
CV	Coefficient of Variation
CV_b/CV_w	Coefficient of Variation (Between)/Coefficient of Variation (Within)
DAIDS	Division of Acquired Immune Deficiency Syndrome
DBF	Database Freeze
DBR	Database Release
DTG	Dolutegravir
FD	Food Effect
GSK	GlaxoSmithKline
HARP	Harmonized Analysis and Reporting Process
IDSL	Integrated Data Standards Library
λz	Terminal phase rate constant
LLQ	Lower limit of quantification
NC	Not Calculable

NQ	Non-quantifiable concentration measured as below LLQ
PK	Pharmacokinetic
QSci	Quantitative Sciences
RAP	Reporting and Analysis Plan
RTF	Rich Text Format
3TC	Lamivudine, EPIVIR™
SAS	Statistical Analysis System
SD	Standard deviation
SDTM	Study Data Tabulation Model
SRP	Statistics Resourcing and Programming
t	time of last quantifiable concentration
$t_{½}$	Terminal phase half-life
t_{lag}	Absorption lag time
T_{max}	Time of occurrence of Cmax
λz	Apparent elimination rate constant
Vz/F	Apparent oral volume of distribution

10.10.2. Trademarks

Trademarks of ViiV Healthcare
EPIVIR
EPZICOM
TIVICAY
TRIUMEQ
TRIZIVIR

Trademarks not owned by ViiV Healthcare
MedDRA
SAS
WinNonlin

10.11. Appendix 11: List of Data Displays

10.11.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.01 to 1.05	N/A
Pharmacokinetic	2.01 to 2.78* *If Part 2 is conducted, same set of tables will be provided as 2.101 to 2.178 with Part 1 and Part 2 indication in the titles	2.01 to 2.44* *If Part 2 is conducted, same set of figures will be provided as 2.101 to 2.144 with Part 1 and Part 2 indication in the titles
Safety	3.01 to 3.13* *If Part 2 is conducted, same set of tables will be provided as 3.101 to 3.113 with Part 1 and Part 2 indication in the titles	N/A
Section	**Listings*** *If Part 2 is conducted, same set of listings will be provided as 101 to 148 with Part 1 and Part 2 indication in the titles	
ICH Listings	1 to 25	
Other Listings	26 to 48	

10.11.2. Mock Example Referencing

Non IDSL specifications will be referenced as indicated and if required an example mock-up displays provided in Appendix 12: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	N/A	N/A	N/A
Pharmacokinetic	PK_F1, PK_F2	PK_T1, PK_T2, PK_T3, PK_T4, PK_T5	N/A
Safety	N/A	SAFE_T1	SAFE_L1

NOTES:

- Indicate display is Non-Standard in the 'IDSL/TST ID / Example Shell' or 'Programming Notes' column.

10.11.3. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.01	Safety	CP_ES1 (XO)	Summary of Subject Disposition	Include Part 2 and Total (if Part 2 is conducted)	SAC
Demographics					
1.02	Safety	DM3 (XO)	Summary of Demographic characteristics	Include BMI, Race detail Include Part 2 and Total (if Part 2 is conducted)	SAC
1.03	Safety	DM5	Summary of Race and Racial Combinations	Include Part 2 and Total (if Part 2 is conducted)	SAC
1.04	Safety	DM6	Summary of Race and Racial Combinations Details	Include Part 2 and Total (if Part 2 is conducted)	SAC
1.05	Safety	DV1	Summary of Important Protocol Deviations	Include Part 2 and Total (if Part 2 is conducted)	SAC

10.11.4. Pharmacokinetic Tables

If Part 2 is conducted, same set of tables will be provided as 2.101 to 2.178 with Part 1 and Part 2 indication in the titles

Pharmacokinetic Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentration Data					
2.01	PK Parameter BE Summary	pkct1	Summary of DTG Plasma Concentration-time Data (unit) by Treatment - Bioequivalence Assessment	Treatments A, B only	SAC
2.02	PK Parameter BE Summary	pkct1	Summary of 3TC Plasma Concentration-time Data (unit) by Treatment - Bioequivalence Assessment	Treatments A, B only	SAC
2.03	PK Parameter FD Summary	pkct1	Summary of DTG Plasma Concentration-time Data (unit) by Treatment - Food Effect	Treatments B, B_Fed only	SAC
2.04	PK Parameter FD Summary	pkct1	Summary of 3TC Plasma Concentration-time Data (unit) by Treatment – Food Effect	Treatments B, B_Fed only	SAC
2.05	PK Plasma Concentration	pkct1	Summary of DTG Plasma Concentration-time Data (unit) by Treatment	All 3 treatments in the same table	SAC
2.06	PK Plasma Concentration	pkct1	Summary of 3TC Plasma Concentration-time Data (unit) by Treatment	All 3 treatments in the same table	SAC

Pharmacokinetic Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Derived Parameters based on Actual Sampling Time					
2.07	PK Parameter BE Summary	pkpt1	Summary of Untransformed DTG Plasma PK Parameters based on Actual Sampling Time - Bioequivalence Assessment	All parameters with units; Treatments A, B only	SAC
2.08	PK Parameter BE Summary	pkpt1	Summary of Untransformed 3TC Plasma PK Parameters based on Actual Sampling Time - Bioequivalence Assessment	All parameters with units; Treatments A, B only	SAC
2.09	PK Parameter BE Summary	pkpt3	Summary of Log_e-transformed DTG Plasma PK Parameters based on Actual Sampling Time - Bioequivalence Assessment	Parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, C_t, CL/F and $t_{1/2}$ with units; Treatments A, B only	SAC
2.10	PK Parameter BE Summary	pkpt3	Summary of Log_e-transformed 3TC Plasma PK Parameters based on Actual Sampling Time - Bioequivalence Assessment	Parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, C_t, CL/F and $t_{1/2}$ with units; Treatments A, B only	SAC
2.11	PK Parameter FD Summary	pkpt1	Summary of Untransformed DTG Plasma PK Parameters based on Actual Sampling Time - Food Effect	All parameters with units; Treatments B, B_Fed only	SAC
2.12	PK Parameter FD Summary	pkpt1	Summary of Untransformed 3TC Plasma PK Parameters based on Actual Sampling Time - Food Effect	All parameters with units; Treatments B, B_Fed only	SAC

Pharmacokinetic Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.13	PK Parameter FD Summary	pkpt3	Summary of Log_e-transformed DTG Plasma PK Parameters based on Actual Sampling Time - Food Effect	Parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, C_t, CL/F and $t_{1/2}$ with units; Treatments B, B_Fed only	SAC
2.14	PK Parameter FD Summary	pkpt3	Summary of Log_e-transformed 3TC Plasma PK Parameters based on Actual Sampling Time - Food Effect	Parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, C_t, CL/F and $t_{1/2}$ with units; Treatments B, B_Fed only	SAC
2.15	PK Plasma Concentration	pkpt1	Summary of Untransformed DTG Plasma PK Parameters based on Actual Sampling Time	All parameters with units; All treatments	SAC
2.16	PK Plasma Concentration	pkpt1	Summary of Untransformed 3TC Plasma PK Parameters based on Actual Sampling Time	All parameters with units; All treatments	SAC
2.17	PK Plasma Concentration	pkpt3	Summary of Log_e-transformed DTG Plasma PK Parameters based on Actual Sampling Time	Parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, C_t, CL/F and $t_{1/2}$ with units; All treatments	SAC
2.18	PK Plasma Concentration	pkpt3	Summary of Log_e-transformed 3TC Plasma PK Parameters based on Actual Sampling Time	Parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, C_t, CL/F and $t_{1/2}$ with units; All treatments	SAC

Pharmacokinetic Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Statistical Analysis Table based on Actual Sampling Time					
2.19	PK Parameter BE Summary	PK_T1	Summary of Statistical Analysis of Log_e-transformed DTG Plasma PK Parameters based on Actual Sampling Time - Bioequivalence Assessment	Parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$ with units; Treatments A, B only	SAC
2.20	PK Parameter BE Summary	PK_T1	Summary of Statistical Analysis of Log_e-transformed 3TC Plasma PK Parameters based on Actual Sampling Time - Bioequivalence Assessment	Parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$ with units; Treatments A, B only	SAC
2.21	PK Parameter BE Summary	PK_T2	Summary of Statistical Analysis of Untransformed DTG Plasma PK Parameters based on Actual Sampling Time - Bioequivalence Assessment	Parameters t_{lag} and T_{max} with units; Treatments A, B only	SAC
2.22	PK Parameter BE Summary	PK_T2	Summary of Statistical Analysis of Untransformed 3TC Plasma PK Parameters based on Actual Sampling Time - Bioequivalence Assessment	Parameters t_{lag} and T_{max} with units; Treatments A, B only	SAC
2.23	PK Parameter BE Summary	MID201676, Table 2.17	Summary of Type 3 Tests of Fixed Effects for Log_e-transformed PK Parameters based on Actual Sampling Time - Bioequivalence Assessment	Parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$ with units; Treatments A, B only	SAC
2.24	PK Parameter BE Summary	MID201676, Table 2.18	Summary of Variance Estimates Effects for PK Parameters based on Actual Sampling Time - Bioequivalence Assessment	Parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$ with units; Treatments A, B only	SAC

Pharmacokinetic Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.25	PK Parameter FD Summary	PK_T1	Summary of Statistical Analysis of Log_e-transformed DTG Plasma PK Parameters based on Actual Sampling Time - Food Effect	Parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$ with units; Treatments B, B_Fed only	SAC
2.26	PK Parameter FD Summary	PK_T1	Summary of Statistical Analysis of Log_e-transformed 3TC Plasma PK Parameters based on Actual Sampling Time - Food Effect	Parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$ with units; Treatments B, B_Fed only	SAC
2.27	PK Parameter FD Summary	PK_T2	Summary of Statistical Analysis of Untransformed DTG Plasma PK Parameters based on Actual Sampling Time – Food Effect	Parameters t_{lag} and T_{max} with units; Treatments B, B_Fed only	SAC
2.28	PK Parameter FD Summary	PK_T2	Summary of Statistical Analysis of Untransformed 3TC Plasma PK Parameters based on Actual Sampling Time – Food Effect	Parameters t_{lag} and T_{max} with units; Treatments B, B_Fed only	SAC
2.29	PK Parameter FD Summary	MID201676, Table 2.17	Summary of Type 3 Tests of Fixed Effects for Log_e-transformed PK Parameters based on Actual Sampling Time - Food Effect	Parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$ with units; Treatments B, B_Fed only	SAC
2.30	PK Parameter FD Summary	MID201676, Table 2.18	Summary of Variance Estimates Effects for PK Parameters based on Actual Sampling Time - Food Effect	Parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$ with units; Treatments B, B_Fed	SAC

Pharmacokinetic Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Derived Parameters based on Nominal Sampling Time					
2.31	PK Parameter BE Summary	pkpt1	Summary of Untransformed DTG Plasma PK Parameters based on Nominal Sampling Time - Bioequivalence Assessment	All parameters with units; Treatments A, B only	SAC
2.32	PK Parameter BE Summary	pkpt1	Summary of Untransformed 3TC Plasma PK Parameters based on Nominal Sampling Time - Bioequivalence Assessment	All parameters with units; Treatments A, B only	SAC
2.33	PK Parameter BE Summary	pkpt3	Summary of Log_e-transformed DTG Plasma PK Parameters based on Nominal Sampling Time - Bioequivalence Assessment	Parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, C_t, CL/F and $t_{1/2}$ with units; Treatments A, B only	SAC
2.34	PK Parameter BE Summary	pkpt3	Summary of Log_e-transformed 3TC Plasma PK Parameters based on Nominal Sampling Time - Bioequivalence Assessment	Parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, C_t, CL/F and $t_{1/2}$ with units;Treatments A, B only	SAC
2.35	PK Parameter FD Summary	pkpt1	Summary of Untransformed DTG Plasma PK Parameters based on Nominal Sampling Time - Food Effect	All parameters with units; Treatments B, B_Fed only	SAC
2.36	PK Parameter FD Summary	pkpt1	Summary of Untransformed 3TC Plasma PK Parameters based on Nominal Sampling Time - Food Effect	All parameters with units; Treatments B, B_Fed only	SAC
2.37	PK Parameter FD Summary	pkpt3	Summary of Log_e-transformed DTG Plasma PK Parameters based on Nominal Sampling Time - Food Effect	Parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, C_t, CL/F and $t_{1/2}$ with units;Treatments B, B_Fed only	SAC

Pharmacokinetic Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.38	PK Parameter FD Summary	pkpt3	Summary of Log_e-transformed 3TC Plasma PK Parameters based on Nominal Sampling Time - Food Effect	Parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, C_t, CL/F and $t_{1/2}$ with units; Treatments B, B_Fed only	SAC
2.39	PK Plasma Concentration	pkpt1	Summary of Untransformed DTG Plasma PK Parameters based on Nominal Sampling Time	All parameters with units; All treatments	SAC
2.40	PK Plasma Concentration	pkpt1	Summary of Untransformed 3TC Plasma PK Parameters based on Nominal Sampling Time	All parameters with units; All treatments	SAC
2.41	PK Plasma Concentration	pkpt3	Summary of Log_e-transformed DTG Plasma PK Parameters based on Nominal Sampling Time	Parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, C_t, CL/F and $t_{1/2}$ with units; All treatments	SAC
2.42	PK Plasma Concentration	pkpt3	Summary of Log_e-transformed 3TC Plasma PK Parameters based on Nominal Sampling Time	Parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, C_t, CL/F and $t_{1/2}$ with units; All treatments	SAC
Statistical Analysis Table based on Nominal Sampling Time					
2.43	PK Parameter BE Summary	PK_T1	Summary of Statistical Analysis of Log_e-transformed DTG Plasma PK Parameters based on Nominal Sampling Time - Bioequivalence Assessment	Parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$ with units; Treatments A, B only	IA (only $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, C_{max}) SAC

Pharmacokinetic Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.44	PK Parameter BE Summary	PK_T1	Summary of Statistical Analysis of Log_e-transformed 3TC Plasma PK Parameters based on Nominal Sampling Time - Bioequivalence Assessment	Parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$ with units; Treatments A, B only	IA (only $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, C_{max}) SAC
2.45	PK Parameter BE Summary	PK_T2	Summary of Statistical Analysis of Untransformed DTG Plasma PK Parameters based on Nominal Sampling Time - Bioequivalence Assessment	Parameters tlag and Tmax with units; Treatments A, B only	SAC
2.46	PK Parameter BE Summary	PK_T2	Summary of Statistical Analysis of Untransformed 3TC Plasma PK Parameters based on Nominal Sampling Time - Bioequivalence Assessment	Parameters tlag and Tmax with units; Treatments A, B only	SAC
2.47	PK Parameter BE Summary	MID201676, Table 2.17	Summary of Type 3 Tests of Fixed Effects for Log_e-transformed PK Parameters based on Nominal Sampling Time - Bioequivalence Assessment	Parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$ with units;Treatments A, B only	SAC
2.48	PK Parameter BE Summary	MID201676, Table 2.18	Summary of Variance Estimates Effects for PK Parameters based on Nominal Sampling Time - Bioequivalence Assessment	Parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$ with units; Treatments A, B only	SAC
2.49	PK Parameter FD Summary	PK_T1	Summary of Statistical Analysis of Log_e-transformed DTG Plasma PK Parameters based on Nominal Sampling Time - Food Effect	Parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$ with units; Treatments B, B_Fed only	IA (only $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, C_{max}) SAC

Pharmacokinetic Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.50	PK Parameter FD Summary	PK_T1	Summary of Statistical Analysis of Log_e-transformed 3TC Plasma PK Parameters based on Nominal Sampling Time - Food Effect	Parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$ with units; Treatments B, B_Fed only	IA (only $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, C_{max}) SAC
2.51	PK Parameter FD Summary	PK_T2	Summary of Statistical Analysis of Untransformed DTG Plasma PK Parameters based on Nominal Sampling Time – Food Effect	Parameters t_{lag} and T_{max} with units; Treatments B, B_Fed only	SAC
2.52	PK Parameter FD Summary	PK_T2	Summary of Statistical Analysis of Untransformed 3TC Plasma PK Parameters based on Nominal Sampling Time – Food Effect	Parameters t_{lag} and T_{max} with units; Treatments B, B_Fed only	SAC
2.53	PK Parameter FD Summary	ING114580, Table 3.10	Summary of Type 3 Tests of Fixed Effects for Log_e-transformed PK Parameters based on Nominal Sampling Time - Food Effect	Parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$ with units; Treatments B, B_Fed only	SAC
2.54	PK Parameter FD Summary	ING114580, Table 3.11	Summary of Variance Estimates Effects for PK Parameters based on Nominal Sampling Time - Food Effect	Parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$ with units; Treatments B, B_Fed only	SAC
Canada Specific PK Tables					
PK Concentration Data					
2.55	PK Plasma Concentration	PK_T3	DTG Drug Concentration (unit) for the Test Formulation B		SAC

Pharmacokinetic Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.56	PK Plasma Concentration	PK_T3	DTG Drug Concentration (unit) for the Test Formulation B_Fed		SAC
2.57	PK Plasma Concentration	PK_T3	DTG Drug Concentration (unit) for the Reference Formulation A		SAC
2.58	PK Plasma Concentration	PK_T3	3TC Drug Concentration (unit) for the Test Formulation B		SAC
2.59	PK Plasma Concentration	PK_T3	3TC Drug Concentration (unit) for the Test Formulation B_Fed		SAC
2.60	PK Plasma Concentration	PK_T3	3TC Drug Concentration (unit) for the Reference Formulation A		SAC
PK Derived Parameters based on Actual Sampling Time					
2.61	PK Plasma Concentration	PK_T4	DTG Parameter Estimates based on Actual Time for Each Subject Given the Test Formulation B	All parameters with units	SAC
2.62	PK Plasma Concentration	PK_T4	DTG Parameter Estimates based on Actual Time for Each Subject Given the Test Formulation B_Fed	All parameters with units	SAC
2.63	PK Plasma Concentration	PK_T4	DTG Parameter Estimates based on Actual Time for Each Subject Given the Reference Formulation A	All parameters with units	SAC
2.64	PK Plasma Concentration	PK_T4	3TC Parameter Estimates based on Actual Time for Each Subject Given the Test Formulation B	All parameters with units	SAC
2.65	PK Plasma Concentration	PK_T4	3TC Parameter Estimates based on Actual Time for Each Subject Given the Test Formulation B_Fed	All parameters with units	SAC
2.66	PK Plasma Concentration	PK_T4	3TC Parameter Estimates based on Actual Time for Each Subject Given the Reference Formulation A	All parameters with units	SAC

Pharmacokinetic Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.67	PK Parameter BE Summary	PK_T4	DTG Parameter Estimates based on Actual Time for Each Subject Given the Test Formulation B - Bioequivalence Assessment	All parameters with units	SAC
2.68	PK Parameter BE Summary	PK_T4	DTG Parameter Estimates based on Actual Time for Each Subject Given the Reference Formulation A - Bioequivalence Assessment	All parameters with units	SAC
2.69	PK Parameter BE Summary	PK_T4	3TC Parameter Estimates based on Actual Time for Each Subject Given the Test Formulation B - Bioequivalence Assessment	All parameters with units	SAC
2.70	PK Parameter BE Summary	PK_T4	3TC Parameter Estimates based on Actual Time for Each Subject Given the Reference Formulation A - Bioequivalence Assessment	All parameters with units	SAC
2.71	PK Parameter BE Summary	PK_T5	DTG Parameter Analysis – Data based on Actual Time - Bioequivalence Assessment	All parameters with units; Treatments A, B only	SAC
2.72	PK Parameter BE Summary	PK_T5	3TC Parameter Analysis – Data based on Actual Time - Bioequivalence Assessment	All parameters with units; Treatments A, B only	SAC
2.73	PK Parameter FD Summary	PK_T4	DTG Parameter Estimates based on Actual Time for Each Subject Given the Test Formulation B_Fed – Food Effect	All parameters with units	SAC
2.74	PK Parameter FD Summary	PK_T4	DTG Parameter Estimates based on Actual Time for Each Subject Given the Reference Formulation A – Food Effect	All parameters with units	SAC
2.75	PK Parameter FD Summary	PK_T4	3TC Parameter Estimates based on Actual Time for Each Subject Given the Test Formulation B_Fed – Food Effect	All parameters with units	SAC

Pharmacokinetic Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.76	PK Parameter FD Summary	PK_T4	3TC Parameter Estimates based on Actual Time for Each Subject Given the Reference Formulation A – Food Effect	All parameters with units	SAC
2.77	PK Parameter FD Summary	PK_T5	DTG Parameter Analysis – Data based on Actual Time - Food Effect	All parameters with units; Treatments B, B_Fed only	SAC
2.78	PK Parameter FD Summary	PK_T5	3TC Parameter Analysis – Data based on Actual Time - Food Effect	All parameters with units; Treatments B, B_Fed only	SAC

10.11.5. Pharmacokinetic Figures

If Part 2 is conducted, same set of figures will be provided as 2.101 to 2.144 with Part 1 and Part 2 indication in the titles

Pharmacokinetic Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Individual Concentration Plots					
2.01	PK Plasma Concentration	pkcf1x	Individual Subject DTG Plasma Concentration-time Plot (Linear and Semi-log) by Subject	Paged by Subject	SAC
2.02	PK Plasma Concentration	pkcf1x	Individual Subject 3TC Plasma Concentration-time Plot (Linear and Semi-log) by Subject	Paged by Subject	SAC
2.03	PK Plasma Concentration	pkcf6	Individual Subject DTG Plasma Concentration-time Plot (Linear and Semi-log) by Treatment	Paged by Treatment	SAC
2.04	PK Plasma Concentration	pkcf6	Individual Subject 3TC Plasma Concentration-time Plot (Linear and Semi-log) by Treatment	Paged by Treatment	SAC

Pharmacokinetic Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Mean / Median Concentration Plots					
2.05	PK Parameter BE Summary	pkcf4	Arithmetic Mean (+SD) DTG Plasma Concentration-time Plot (Linear and Semi-log) - Bioequivalence Assessment	Use nominal times in X Axis, Paged by Treatment. Treatments A, B only	SAC
2.06	PK Parameter BE Summary	pkcf4	Arithmetic Mean (+SD) 3TC Plasma Concentration-time Plot (Linear and Semi-log) - Bioequivalence Assessment	Use nominal times in X Axis, Paged by Treatment. Treatments A, B only	SAC
2.07	PK Parameter BE Summary	pkcf5	Median (range) DTG Plasma Concentration-time Plot (Linear and Semi-log) - Bioequivalence Assessment	Use nominal times in X Axis, Paged by Treatment. Treatments A, B only	SAC
2.08	PK Parameter BE Summary	pkcf5	Median (range) 3TC Plasma Concentration-time Plot (Linear and Semi-log) - Bioequivalence Assessment	Use nominal times in X Axis, Paged by Treatment. Treatments A, B only	SAC
2.09	PK Parameter BE Summary	pkcf4	Arithmetic Mean DTG Plasma Concentration-time Plot (Linear and Semi-log) - Bioequivalence Assessment	Use nominal times in X Axis. Keep all the treatments in one plot. Use different colours for different treatments. Treatments A, B only	SAC
2.10	PK Parameter BE Summary	pkcf4	Arithmetic Mean 3TC Plasma Concentration-time Plot (Linear and Semi-log) - Bioequivalence Assessment	Use nominal times in X Axis. Keep all the treatments in one plot. Use different colours for different treatments. Treatments A, B only	SAC

Pharmacokinetic Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.11	PK Parameter BE Summary	pkcf5	Median DTG Plasma Concentration-time Plot (Linear and Semi-log) - Bioequivalence Assessment	Use nominal times in X Axis. Keep all the treatments in one plot. Use different colours for different treatments. Treatments A, B only	SAC
2.12	PK Parameter BE Summary	pkcf5	Median 3TC Plasma Concentration-time Plot (Linear and Semi-log)- Bioequivalence Assessment	Use nominal times in X Axis. Keep all the treatments in one plot. Use different colours for different treatments. Treatments A, B only	SAC
2.13	PK Parameter FD Summary	pkcf4	Arithmetic Mean (+SD) DTG Plasma Concentration-time Plot (Linear and Semi-log) - Food Effect	Use nominal times in X Axis, Paged by Treatment. Treatments B, B_Fed only	SAC
2.14	PK Parameter FD Summary	pkcf4	Arithmetic Mean (+SD) 3TC Plasma Concentration-time Plot (Linear and Semi-log) - Food Effect	Use nominal times in X Axis, Paged by Treatment. Treatments B, B_Fed only	SAC
2.15	PK Parameter FD Summary	pkcf5	Median (range) DTG Plasma Concentration-time Plot (Linear and Semi-log) - Food Effect	Use nominal times in X Axis, Paged by Treatment. Treatments B, B_Fed only	SAC
2.16	PK Parameter FD Summary	pkcf5	Median (range) 3TC Plasma Concentration-time Plot (Linear and Semi-log) - Food Effect	Use nominal times in X Axis, Paged by Treatment. Treatments B, B_Fed only	SAC

Pharmacokinetic Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.17	PK Parameter FD Summary	pkcf4	Arithmetic Mean DTG Plasma Concentration-time Plot (Linear and Semi-log) - Food Effect	Use nominal times in X Axis. Keep all the treatments in one plot. Use different colours for different treatments. Treatments B, B_Fed only	SAC
2.18	PK Parameter FD Summary	pkcf4	Arithmetic Mean 3TC Plasma Concentration-time Plot (Linear and Semi-log) - Food Effect	Use nominal times in X Axis. Keep all the treatments in one plot. Use different colours for different treatments. Treatments B, B_Fed only	SAC
2.19	PK Parameter FD Summary	pkcf5	Median DTG Plasma Concentration-time Plot (Linear and Semi-log) - Food Effect	Use nominal times in X Axis. Keep all the treatments in one plot. Use different colours for different treatments. Treatments B, B_Fed only	SAC
2.20	PK Parameter FD Summary	pkcf5	Median 3TC Plasma Concentration-time Plot (Linear and Semi-log) - Food Effect	Use nominal times in X Axis. Keep all the treatments in one plot. Use different colours for different treatments. Treatments B, B_Fed only	SAC
Comparative PK Parameters Plots based on Actual Sampling Time					
2.21	PK Parameter BE Summary	pkpf3	Comparative Plot of Individual Subject DTG Plasma Pharmacokinetic Parameter based on Actual Sampling Time Versus Treatment - Bioequivalence Assessment	Parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$ with units; Treatments A, B only	SAC

Pharmacokinetic Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.22	PK Parameter BE Summary	pkpf3	Comparative Plot of Individual Subject 3TC Plasma Pharmacokinetic Parameter based on Actual Sampling Time Versus Treatment - Bioequivalence Assessment	Parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$ with units; Treatments A, B only	SAC
2.23	PK Parameter BE Summary	PK_F1	Treatment Comparative Plot of Adjusted Geometric Mean (95% CI) with Individual Subjects DTG Plasma Pharmacokinetic Parameters based on Actual Sampling Time - Bioequivalence Assessment	Paged by $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$ with units; Treatments A, B only	SAC
2.24	PK Parameter BE Summary	PK_F1	Treatment Comparative Plot of Adjusted Geometric Mean (95% CI) with Individual Subjects 3TC Plasma Pharmacokinetic Parameters based on Actual Sampling Time - Bioequivalence Assessment	Paged by $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$ with units; Treatments A, B only	SAC
2.25	PK Parameter FD Summary	pkpf3	Comparative Plot of Individual Subject DTG Plasma Pharmacokinetic Parameter based on Actual Sampling Time Versus Treatment – Food Effect	Parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$ with units; Treatments B, B_Fed only	SAC
2.26	PK Parameter FD Summary	pkpf3	Comparative Plot of Individual Subject 3TC Plasma Pharmacokinetic Parameter based on Actual Sampling Time Versus Treatment – Food Effect	Parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$ with units; Treatments B, B_Fed only	SAC

Pharmacokinetic Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.27	PK Parameter FD Summary	PK_F1	Treatment Comparative Plot of Adjusted Geometric Mean (95% CI) with Individual Subjects DTG Plasma Pharmacokinetic Parameters based on Actual Sampling Time – Food Effect	Paged by $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$ with units; Treatments B, B_Fed only	SAC
2.28	PK Parameter FD Summary	PK_F1	Treatment Comparative Plot of Adjusted Geometric Mean (95% CI) with Individual Subjects 3TC Plasma Pharmacokinetic Parameters based on Actual Sampling Time – Food Effect	Paged by $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$ with units; Treatments B, B_Fed only	SAC
Statistical Analysis Plots based on Actual Sampling Time					
2.29	PK Parameter BE Summary	PK_F2	Geometric Mean Treatment Ratio and 90% CI of DTG Plasma Pharmacokinetic Parameters based on Actual Sampling Time - Bioequivalence Assessment	Produce for $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$, all parameters on one plot. Treatments A, B only	SAC
2.30	PK Parameter BE Summary	PK_F2	Geometric Mean Treatment Ratio and 90% CI of 3TC Plasma Pharmacokinetic Parameters based on Actual Sampling Time - Bioequivalence Assessment	Produce for $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$, all parameters on one plot. Treatments A, B only	SAC
2.31	PK Parameter FD Summary	PK_F2	Geometric Mean Treatment Ratio and 90% CI of DTG Plasma Pharmacokinetic Parameters based on Actual Sampling Time – Food Effect	Produce for $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$, all parameters on one plot. Treatments B, B_Fed only	SAC

Pharmacokinetic Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.32	PK Parameter FD Summary	PK_F2	Geometric Mean Treatment Ratio and 90% CI of 3TC Plasma Pharmacokinetic Parameters based on Actual Sampling Time – Food Effect	Produce for $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$, all parameters on one plot. Treatments B, B_Fed only	SAC
Comparative PK Parameters Plots based on Nominal Sampling Time					
2.33	PK Parameter BE Summary	pkpf3	Comparative Plot of Individual Subject DTG Plasma Pharmacokinetic Parameter based on Nominal Sampling Time Versus Treatment - Bioequivalence Assessment	Parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$ with units; Treatments A, B only	SAC
2.34	PK Parameter BE Summary	pkpf3	Comparative Plot of Individual Subject 3TC Plasma Pharmacokinetic Parameter based on Nominal Sampling Time Versus Treatment - Bioequivalence Assessment	Parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$ with units; Treatments A, B only	SAC
2.35	PK Parameter BE Summary	PK_F1	Treatment Comparative Plot of Adjusted Geometric Mean (95% CI) with Individual Subjects DTG Plasma Pharmacokinetic Parameters based on Nominal Sampling Time - Bioequivalence Assessment	Paged by $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$ with units; Treatments A, B only	SAC
2.36	PK Parameter BE Summary	PK_F1	Treatment Comparative Plot of Adjusted Geometric Mean (95% CI) with Individual Subjects 3TC Plasma Pharmacokinetic Parameters based on Nominal Sampling Time - Bioequivalence Assessment	Paged by $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$ with units; Treatments A, B only	SAC

Pharmacokinetic Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.37	PK Parameter FD Summary	pkpf3	Comparative Plot of Individual Subject DTG Plasma Pharmacokinetic Parameter based on Nominal Sampling Time Versus Treatment – Food Effect	Parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$ with units; Treatments B, B_Fed only	SAC
2.38	PK Parameter FD Summary	pkpf3	Comparative Plot of Individual Subject 3TC Plasma Pharmacokinetic Parameter based on Nominal Sampling Time Versus Treatment – Food Effect	Parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$ with units; Treatments B, B_Fed only	SAC
2.39	PK Parameter FD Summary	PK_F1	Treatment Comparative Plot of Adjusted Geometric Mean (95% CI) with Individual Subjects DTG Plasma Pharmacokinetic Parameters based on Nominal Sampling Time – Food Effect	Paged by $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$ with units; Treatments B, B_Fed only	SAC
2.40	PK Parameter FD Summary	PK_F1	Treatment Comparative Plot of Adjusted Geometric Mean (95% CI) with Individual Subjects 3TC Plasma Pharmacokinetic Parameters based on Nominal Sampling Time – Food Effect	Paged by $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$ with units; Treatments B, B_Fed only	SAC
Statistical Analysis Plots based on Nominal Sampling Time					
2.41	PK Parameter BE Summary	PK_F2	Geometric Mean Treatment Ratio and 90% CI of DTG Plasma Pharmacokinetic Parameters based on Nominal Sampling Time - Bioequivalence Assessment	Produce for $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$, all parameters on one plot. Treatments A, B only	SAC

Pharmacokinetic Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.42	PK Parameter BE Summary	PK_F2	Geometric Mean Treatment Ratio and 90% CI of 3TC Plasma Pharmacokinetic Parameters based on Nominal Sampling Time - Bioequivalence Assessment	Produce for $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$, all parameters on one plot. Treatments A, B only	SAC
2.43	PK Parameter FD Summary	PK_F2	Geometric Mean Treatment Ratio and 90% CI of DTG Plasma Pharmacokinetic Parameters based on Nominal Sampling Time – Food Effect	Produce for $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$, all parameters on one plot. Treatments B, B_Fed only	SAC
2.44	PK Parameter FD Summary	PK_F2	Geometric Mean Treatment Ratio and 90% CI of 3TC Plasma Pharmacokinetic Parameters based on Nominal Sampling Time – Food Effect	Produce for $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, C_{max}, C_{24}, CL/F and $t_{1/2}$, all parameters on one plot. Treatments B, B_Fed only	SAC

10.11.6. Safety Tables

If Part 2 is conducted, same set of tables will be provided as 3.101 to 3.113 with Part 1 and Part 2 indication in the titles

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
3.01	Safety	CP_AE1x (xo)	Summary of All Adverse Events		SAC
3.02	Safety	CP_AE1x (xo)	Summary of Drug-Related Adverse Events		SAC
3.03	Safety	CP_AE1x (xo)	Summary of Serious Adverse Events		SAC
3.04	Safety	CP_AE1x (xo)	Summary of AEs Leading to Permanent Discontinuation of Study Drug or Withdrawal from Study		SAC
Labs					
3.05	Safety	LB1	Summary of Chemistry Laboratory Values		SAC
3.06	Safety	LB1	Summary of Change from Baseline for Chemistry Laboratory Values		SAC
3.07	Safety	LB1	Summary of Hematology Laboratory Values		SAC
3.08	Safety	LB1	Summary of Change from Baseline for Hematology Laboratory Values		SAC
ECGs					
3.09	Safety	EG1	Summary of ECG Findings		SAC
3.10	Safety	EG2	Summary of ECG Values		SAC
Vital Signs					
3.11	Safety	VS1	Summary of Vital Signs	Include BP, HR	SAC

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.12	Safety	VS1	Summary of Change From Baseline for Vital Signs	Include BP, HR	SAC
3.13	Safety	SAFE_T1	Frequency of Subjects with Vital Signs Measurements Outside the Potential Clinical Concern Range		SAC

10.11.7. ICH Listings

If Part 2 is conducted, same set of listings will be provided as 101 to 148 with Part 1 and Part 2 indication in the titles

ICH Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Randomisation					
1	Safety	CP_RA1x (XO)	Listing of Randomized and Actual Treatments	Add randomization date	SAC
Subject Disposition					
2	Screening	ES7	Listing of Reasons for Screening Failures	Include Age and Sex. Concatenate with Subjid	SAC
3	Safety	CP_ES10x (XO)	Listing of Reasons for Withdrawal		SAC
4	Safety	DV2	Listing of Protocol Deviations		SAC
5	Screening	SAFE_L1	Listing of Subjects Excluded from Analysis Populations		SAC
6	Safety	IE4 (XO)	Listing of Subjects with Inclusion/Exclusion Criteria Deviations		SAC
Demographics					
7	Safety	DM4 (XO)	Listing of Demographic Characteristics		SAC
8	Safety	DM10 (XO)	Listing of Race		SAC
Concomitant Medication					
9	Safety	CP_CM4 (XO)	Listing of Concomitant Medications by Generic Term		SAC
Exposure					
10	Safety	EX4 (XO)	Listing of Exposure Data		SAC

ICH Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
11	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events		SAC
12	Safety	CP_AE9 (XO)	Listing of All Adverse Events		SAC
13	Safety	CP_AE9 (XO)	Listing of Drug Related Adverse Events		SAC
14	Safety	CP_AE9a (xo)	Listing of Serious Adverse Events		SAC
15	Safety	CP_AE9 (xo)	Listing of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study		SAC
LABS					
16	Safety	CP_LB6 (xo)	Listing of Clinical Chemistry with Grade 2 or Higher Lab Abnormalities	Include all tests in which we have DAIDS criteria.	SAC
17	Safety	CP_LB6 (xo)	Listing of All Clinical Chemistry Laboratory Data for Subjects with Grade 2 or Higher Lab Abnormalities	Include all tests in which we have DAIDS criteria.	SAC
18	Safety	CP_LB6 (xo)	Listing of Hematology with Grade 2 or Higher Lab Abnormalities	Include all tests in which we have DAIDS criteria.	SAC
19	Safety	CP_LB6 (xo)	Listing of All Hematology Laboratory Data for Subjects with Grade 2 or Higher Lab Abnormalities	Include all tests in which we have DAIDS criteria.	SAC
20	Safety	UR2b	Listing of Urinalysis Data for Subjects with Positive Dipstick or Microscopic Results		SAC

ICH Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
ECGs					
21	Safety	CP_EG4 (xo)	Listing of ECG Values of Potential Clinical Importance		SAC
22	Safety	CP_EG4 (xo)	Listing of All ECG Values for Subjects with any Value of Potential Clinical Importance		SAC
23	Safety	CP_EG6 (xo)	Listing of Abnormal ECG findings		SAC
Vital Signs					
24	Safety	CP_VS5 (XO)	Listing of Vital Signs of Potential Clinical Importance		SAC
25	Safety	CP_VS5 (XO)	Listing of All Vital Signs for Subjects with any Value of Potential Clinical Importance		SAC

10.11.8. Non-ICH Listings

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
AE					
26	Safety	AE2	Relationship between System Organ Class and Verbatim Text		SAC
PK					
27	PK Plasma Concentration	pkcl1x	Listing of DTG Plasma Concentration-time Data		SAC
28	PK Plasma Concentration	pkcl1x	Listing of 3TC Plasma Concentration-time Data		SAC
29	PK Plasma Concentration	pkpl1x	Listing of DTC Plasma PK Parameters based on Actual Sampling Time		SAC
30	PK Plasma Concentration	pkpl1x	Listing of 3TC Plasma PK Parameters based on Actual Sampling Time		SAC
31	PK Plasma Concentration	pkpl1x	Listing of DTC Plasma PK Parameters based on Nominal Sampling Time		SAC
32	PK Plasma Concentration	pkpl1x	Listing of 3TC Plasma PK Parameters based on Nominal Sampling Time		SAC
33	PK Parameter BE Summary	mid20167, listing 33	Listing of Individual DTG Plasma PK Parameter Treatment Ratios based on Actual Sampling Time - Bioequivalence Assessment		SAC
34	PK Parameter BE Summary	mid20167, listing 33	Listing of Individual 3TC Plasma PK Parameter Treatment Ratios based on Actual Sampling Time - Bioequivalence Assessment		SAC

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
35	PK Parameter FD Summary	mid20167, listing 33	Listing of Individual DTG Plasma PK Parameter Treatment Ratios based on Actual Sampling Time – Food Effect		SAC
36	PK Parameter FD Summary	mid20167, listing 33	Listing of Individual 3TC Plasma PK Parameter Treatment Ratios based on Actual Sampling Time – Food Effect		SAC
37	PK Parameter BE Summary	mid20167, listing 33	Listing of Individual DTG Plasma PK Parameter Treatment Ratios based on Nominal Sampling Time - Bioequivalence Assessment		SAC
38	PK Parameter BE Summary	mid20167, listing 33	Listing of Individual 3TC Plasma PK Parameter Treatment Ratios based on Nominal Sampling Time - Bioequivalence Assessment		SAC
39	PK Parameter FD Summary	mid20167, listing 33	Listing of Individual DTG Plasma PK Parameter Treatment Ratios based on Nominal Sampling Time – Food Effect		SAC
40	PK Parameter FD Summary	mid20167, listing 33	Listing of Individual 3TC Plasma PK Parameter Treatment Ratios based on Nominal Sampling Time – Food Effect		SAC
41	PK Parameter BE Summary	N/A	RAW SAS Output from Statistical Analysis of Log_e-transformed DTG Plasma PK Parameters based on Actual Sampling Time - Bioequivalence Assessment		SAC
42	PK Parameter BE Summary	N/A	RAW SAS Output from Statistical Analysis of Log_e-transformed 3TC Plasma PK Parameters based on Actual Sampling Time - Bioequivalence Assessment		SAC

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
43	PK Parameter FD Summary	N/A	RAW SAS Output from Statistical Analysis of Log_e-transformed DTG Plasma PK Parameters based on Actual Sampling Time - Food Effect		SAC
44	PK Parameter FD Summary	N/A	RAW SAS Output from Statistical Analysis of Log_e-transformed 3TC Plasma PK Parameters based on Actual Sampling Time - Food Effect		SAC
45	PK Parameter BE Summary	N/A	RAW SAS Output from Statistical Analysis of Log_e-transformed DTG Plasma PK Parameters based on Nominal Sampling Time - Bioequivalence Assessment		SAC
46	PK Parameter BE Summary	N/A	RAW SAS Output from Statistical Analysis of Log_e-transformed 3TC Plasma PK Parameters based on Nominal Sampling Time - Bioequivalence Assessment		SAC
47	PK Parameter FD Summary	N/A	RAW SAS Output from Statistical Analysis of Log_e-transformed DTG Plasma PK Parameters based on Nominal Sampling Time - Food Effect		SAC
48	PK Parameter FD Summary	N/A	RAW SAS Output from Statistical Analysis of Log_e-transformed 3TC Plasma PK Parameters based on Nominal Sampling Time - Food Effect		SAC

10.12. Appendix 12: Example Mock Shells for Data Displays

Example : PK_T1
Protocol : 204994 Page 1 of n
Population : PK Parameter BE Summary (programming note: 'PK Parameter BE (or FD) Summary' depending each display in TOC)

Table xx.xx

Summary of Statistical Analysis of Log_e-transformed DTG Plasma Pharmacokinetic Parameters based on Actual Sampling Time

Parameter	*Comparison Test vs Reference*	*Adjusted Geometric Mean n Test*	*n Ref*	*Ratio (Test/Ref)*	*90% Confidence Interval for Ratio*	*%CVw*
C_{max}(units)	*[Test treatment description] vs [Reference treatment description]*	*x xx.xx*	*x xx.xx*	*x.xxxx*	*(x.xxxx, x.xxxx)*	*xx.x*
$AUC_{(0-t)}$(units)	*[Test treatment description] vs [Reference treatment description]*	*x xx.xx*	*x xx.xx*	*x.xxxx*	*(x.xxxx, x.xxxx)*	*xx.x*
$AUC_{(0-\infty)}$(units)	*[Test treatment description] vs [Reference treatment description]*	*x xx.xx*	*x xx.xx*	*x.xxxx*	*(x.xxxx, x.xxxx)*	*xx.x*
C_{24}(units)	*[Test treatment description] vs [Reference treatment description]*	*x xx.xx*	*x xx.xx*	*x.xxxx*	*(x.xxxx, x.xxxx)*	*xx.x*

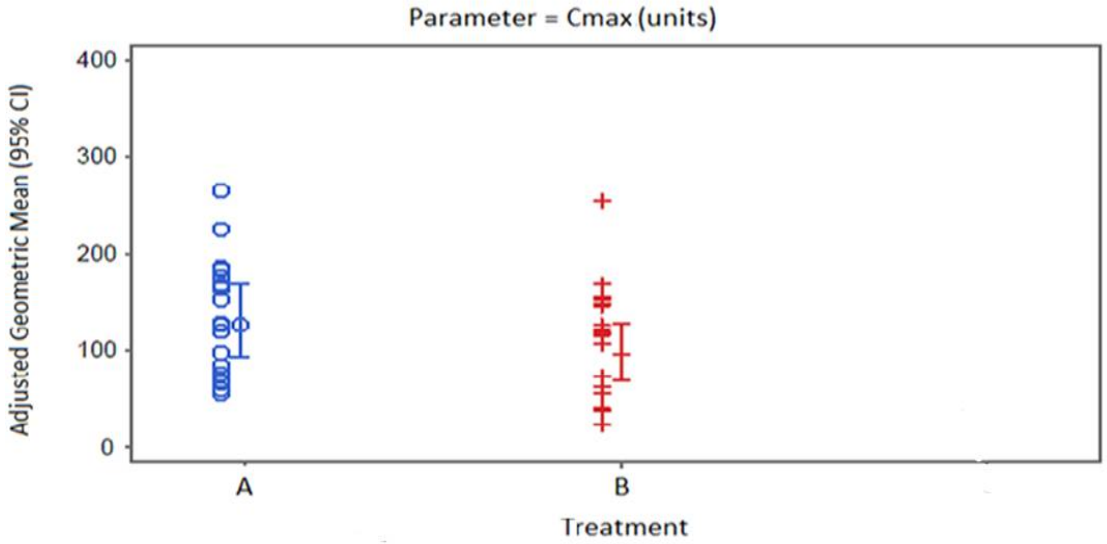
Example : PK_T2
Protocol : 204994 Page 1 of n
Population : PK Parameter BE Summary

Table xx.xx
Summary of Statistical Analysis of Median Difference and Confidence Interval for DTG Pharmacokinetic Parameters based on Actual Sampling Time

Parameter	*Comparison*	*Median*		*Estimated Median Diff*	*90% Confidence*
	Test vs Reference	*n Test*	*n Ref*	*(Test - Ref)*	*Interval for Diff*
T_{lag}(units)	*[Test treatment description] vs [Reference treatment description]*	*x xx.xx*	*x xx.xx*	*x.xxxx*	*(x.xxxx, x.xxxx)*
T_{max})(units)	*[Test treatment description] vs [Reference treatment description]*	*x xx.xx*	*x xx.xx*	*x.xxxx*	*(x.xxxx, x.xxxx)*

Example : PK_*F1*
Protocol : *204994*
Population : PK Parameter BE Summary

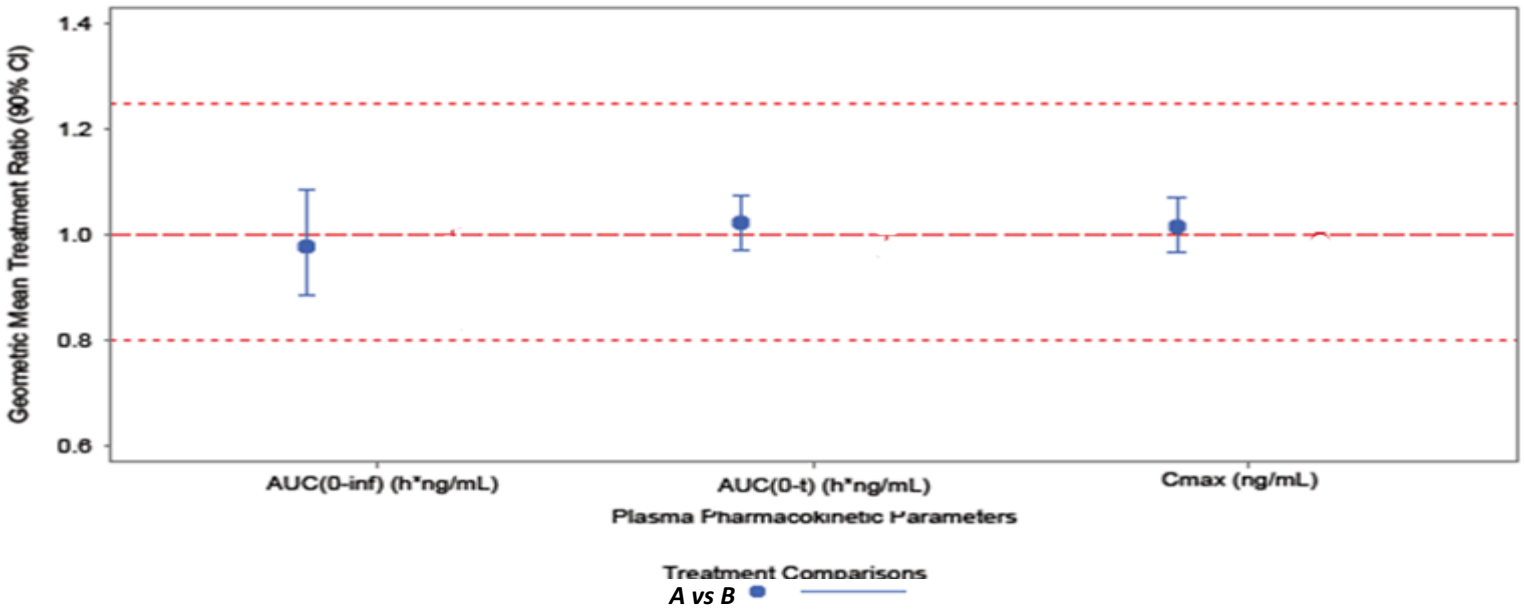
Figure xx.xx
Treatment Comparative Plot of Adjusted Geometric Mean (95% CI) with Individual Subjects
DTG Plasma Pharmacokinetic Parameters



Programming note: add footnote for treatment A, B.

Example : PK_F2
Protocol : 204994
Population : PK Parameter BE Summary

Figure xx.xx
Geometric Mean Treatment Ratio and 90% CI of DTG Plasma Pharmacokinetic Parameters



Note: The reference lines at ratios of 0.80, 1.25 represent BE criterion.

Programming note: add footnote for treatment A, B.

Example: SAFE_T1
Protocol: 204994
Population: Safety

Table xx.xx
Number of Subjects with Change from Baseline Vital Signs Category

VSTEST	Pl. Time	Subject Position	Flagging category	Test (N=XX)	Reference (N=XX)
Diastolic Blood Pressure (mmHg)	Time 1	Supine	n	XX	XX
			Increase >=20	0	XX(XX%)
			Increase >=40	XX(XX%)	0
			Decrease >=20	0	XX(XX%)
			Decrease >=40	XX(XX%)	0
	Time 2	Supine	n	XX	XX
			Increase >=20	0	XX(XX%)
			Increase >=40	XX(XX%)	0
			Decrease >=20	0	XX(XX%)
			Decrease >=40	XX(XX%)	0

Example: SAFE_L1
Protocol: 204994
Population: Screening

Listing X
Listing of Subjects Excluded from Analysis Populations

Population	No. of Subjects	No. of Subjects Excluded	Subject numbers
Screening	xxx	xx	xxx, xxx, xxx, xxx.
Safety	xx	0	
PK Plasma Concentration	xx	xx	xxx
PK Parameter BE Summary	xx	xx	xxx
PK Parameter Food Effect Summary	xx	xx	xxx

Example: PK_T3
Protocol: 204994
Population: PK Plasma Concentration

Table x.xx
DTG Drug Concentration (unit) for the Test Formulation B

ID	Seq	Period	Sampling Times (hours)											
			0.0	0.33	0.66	1.0	1.5	2.0	3.0	4.0	6.0	8.0	12.0	16.0
A	TR	14 May	0.00	BLQ*	52.01	95.03	122.20	77.88	65.15	46.24	19.20	14.99	BLQ*	BLQ*
B	RT	21 May	0.00	BLQ*	56.66	80.85	102.00	86.41	63.81	49.20	24.00	11.37	8.24	BLQ*
C	RT	21 May	0.00	28.63	201.50	189.80	188.70	136.20	97.64	64.53	32.08	20.63	14.59	BLQ*
E	TR	14 May	0.00	BLQ*	9.04	34.32	47.70	52.79	59.47	32.61	17.61	8.76	BLQ*	BLQ*
F	RT	21 May	0.00	BLQ*	55.33	66.40	58.97	48.29	43.19	34.23	17.30	6.15	BLQ*	BLQ*
G	TR	14 May	0.00	BLQ*	33.15	45.64	54.19	34.13	32.78	21.73	10.75	8.35	BLQ*	BLQ*
H	RT	21 May	0.00	35.38	79.14	100.90	70.71	48.43	30.73	26.19	8.65	6.83	BLQ*	BLQ*
I	TR	14 May	0.00	BLQ*	64.57	76.52	89.51	86.21	69.04	50.96	21.55	13.71	7.55	BLQ*
K	RT	21 May	0.00	BLQ*	79.34	99.41	154.80	58.60	57.12	32.57	19.82	BLQ*	BLQ*	BLQ*
L	TR	14 May	0.00	14.78	55.54	56.88	46.87	37.29	28.75	25.20	BLQ*	BLQ*	BLQ*	BLQ*
M	TR	14 May	0.00	BLQ*	BLQ*	BLQ*	BLQ*	BLQ*	8.37	23.15	19.74	16.49	5.74	5.18
N	RT	21 May	0.00	BLQ*	37.76	28.58	21.56	19.02	13.25	12.44	6.38	BLQ*	BLQ*	BLQ*
O	RT	21 May	0.00	BLQ*	27.85	43.30	43.30	32.57	29.59	25.42	16.89	7.68	BLQ*	BLQ*
P	TR	14 May	0.00	BLQ*	68.25	52.57	51.97	28.64	23.70	12.74	BLQ*	BLQ*	BLQ*	BLQ*
Q	RT	21 May	0.00	BLQ*	5.90	13.00	27.54	13.32	12.34	9.81	9.73	BLQ*	BLQ*	BLQ*
R	TR	14 May	0.00	BLQ*	18.92	35.77	53.93	60.43	47.44	41.72	16.66	8.87	5.49	BLQ*
. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
MEAN	-	-	0.00	4.92	52.81	63.69	70.87	51.26	42.65	31.80	15.04	7.73	2.60	0.32
STD	-	-	0.00	11.26	47.05	45.04	49.76	33.66	24.64	15.42	8.60	6.57	4.42	1.29
CV	-	-	-	228.66	89.09	70.72	70.22	65.66	57.79	48.51	57.18	84.94	169.84	400
*	Lower limit of quantitation is 5 ng/mL. Any concentration below this limit is reported as Below Limit of Quantitation (BLQ) except at time 0. Zero is used in the calculation of area under the curve (AUC) for times preceding the first observed concentration and in the calculation of summary statistics.													

Example: PK_T4
Protocol: 204994
Population: PK Plasma Concentration

Table x.xx
DTG Parameter Estimates based on Actual Time for Each Subject Given the Test Formulation B

ID	Seq	Period	TEST FORMULATION								
			C_{max} (ng/mL)	t_{max} (h)	AUCT (ng·h/mL)	AUCI (ng·h/mL)	AUCT (%)	λ (h^{-1})	TLIN (h)	LQCT (h)	$t_{½}$ (h)
A	TR	14 May	122	1.50	365	409	89	0.3002	2.0	8.0	2.3
B	RT	21 May	102	1.50	405	432	94	0.2384	3.0	12.0	2.9
C	RT	21 May	202	0.66	703	774	91	0.1776	4.0	12.0	3.9
E	TR	14 May	59	3.00	233	256	91	0.3680	3.0	8.0	1.9
F	RT	21 May	66	1.00	247	265	93	0.3902	3.0	8.0	1.8
G	TR	14 May	54	1.50	178	205	87	0.2768	3.0	8.0	2.5
H	RT	21 May	101	1.00	246	263	94	0.3437	2.0	8.0	2.0
I	TR	14 May	90	1.50	408	433	94	0.2486	3.0	12.0	2.8
K	RT	21 May	155	1.50	315	372	85	0.3379	3.0	6.0	2.1
L	TR	14 May	57	1.00	140	331	42	0.1318	3.0	4.0	5.3
M	TR	14 May	23	4.00	165	195	85	0.1485	6.0	16.0	4.7
N	RT	21 May	38	0.66	88	113	78	0.2620	2.0	6.0	2.6
O	RT	21 May	43	1.00	183	215	85	0.2671	3.0	8.0	2.6
P	TR	14 May	68	0.66	122	148	83	0.5031	1.5	4.0	1.4
Q	RT	21 May	28	1.50	68	113	60	0.1833	1.5	6.0	3.8
R	TR	14 May	60	2.00	275	292	94	0.2546	3.0	12.0	2.7
. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
MEAN*	-	-	79	1.50	259	301	84	0.2770	3.0	8.0	2.8
STD	-	-	48	0.89	158	164	14	0.0967	1.1	3.3	1.1
CV	-	-	61	59.35	61	54	17	34.92	37.3	38.5	37.9
*	for t_{max}, TLIN, and LQCT, these are medians.										

Example: PK_T5
Protocol: 204994 Page 1 of n
Population: PK Parameter BE Summary

Table x.xx
DTG Parameter Analysis – Data based on Actual Time - Bioequivalence Assessment

ID	Raw Scale			Log Scale	
	Test AUCT	Reference AUCT	Relative AUCT (%)	Test ln(AUCT)	Reference ln(AUCT)
A	365	375	97	5.8998	5.9269
B	405	595	68	6.0038	6.3885
C	703	471	149	6.5553	6.1548
E	233	190	123	5.4510	5.2470
F	247	257	96	5.5093	5.5490
G	178	175	102	5.1817	5.1647
H	246	382	65	5.5053	5.9454
I	408	361	113	6.0112	5.8888
K	315	218	144	5.7525	5.3844
L	140	92	153	4.9416	4.5217
M	165	269	61	5.1059	5.5947
N	88	106	83	4.4773	4.6634
O	183	290	63	5.2094	5.6698
P	122	230	53	4.8040	5.4380
Q	68	144	47	4.2195	4.9698
R	275	344	80	5.6167	5.8406
. . .	. . .	. . .	. . .	. . .	. . .
MEAN	259	281	94	5.3903	5.5217
STD	158	136	35	0.61	0.52
CV	61	48	37	-	-