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

Title	:	Reporting and Analysis Plan for A Phase I, Open-label, Single-dose Study to Investigate the Pharmacokinetics, Safety and Tolerability of Dolutegravir + Rilpivirine (JULUCA™) 50 mg/25 mg tablets in healthy volunteers of Japanese descent
Compound Number	:	GSK3365791
Effective Date	:	13-JUNE-2019

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 212312 [2018N392977_00].
- This RAP will be provided to the study team members to convey the content of the 212312 Statistical Analysis Complete (SAC) deliverable.

RAP Author(s):

Approver	Date
PPD Principal Statistician (Biostatistics)	11-JUN-2019

RAP Team Approvals (Method: E-mail):

Approver	Date	Approval Method
PPD Senior Director, Clinical Pharmacology	12-JUN-2019	E-mail
PPD Clinical Development Director, Global Medical	12-JUN-2019	E-mail
PPD Medical Director, Global Clinical Safety and Pharmacovigilance	12-JUN-2019	E-mail
PPD Principal Clinical Data Manager, Infectious Disease	11-JUN-2019	E-mail
PPD Clinical Development, Infectious Disease	12-JUN-2019	E-mail
PPD Programmer, Clinical Programming	11-JUN-2019	E-mail

Clinical Statistics and Clinical Programming Line Approvals (Method: Pharma TMF eSignature):

Approver	Date	Approval Method
PPD * Statistics Director, Clinical Statistics	13-JUN-2019	e-signature
PPD ** Programming Manager, Clinical Programming	13-JUN-2019	e-signature

*Delegated to PPD, Statistics Leader by PPD, Statistics Director

**Delegated to PPD, Programming Director

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol 212312:

Revision Chronology:		
Original Document Number	04-APR-2019	Original

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There were no changes or deviations to the originally planned statistical analysis specified in the protocol [(Dated: 04/APR/2019)].

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

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To evaluate the PK of DTG and RPV following a single oral dose of DTG/RPV 50 mg/25 mg FDC in healthy, adult Japanese participants.	• Plasma DTG and RPV $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, C_{max}, t_{lag}, t_{max}, t, $t_{½}$, λz, $\%AUC_{ex}$, $AUC_{(0-24)}$, $AUC_{(0-72)}$, CL/F and Vz/F, C_t, and C_{24} following a single oral dose of DTG/RPV 50 mg/25 mg FDC in healthy adult Japanese participants.
Secondary Objectives	**Secondary Endpoints**
• To evaluate the safety and tolerability of DTG/RPV FDC in healthy, adult Japanese participants.	• Safety and tolerability parameters, adverse event (AE) /serious adverse events (SAE), observed and change from baseline clinical laboratory values, and vital sign assessments.

2.3. Study Design

Design Features	• This is a single dose, open-label study in adult Japanese healthy participants to evaluate the PK, safety and tolerability of DTG/RPV 50 mg/25 mg FDC tablets. The study will consist of screening, treatment and follow-up phases.
Dosing	• Enrolled participants will receive the DTG/RPV 50 mg/25 mg FDC tablet as a single oral dose in a fed state.
Time & Events	• Refer to Appendix 2: Schedule of Activities
Treatment Assignment	• A maximum of 16 healthy adult Japanese subjects will be randomized such that a minimum of approximately 13 evaluable subjects complete the study with at least 3 participants of each gender enrolled.
Interim Analysis	• There will be no interim analysis.

See study protocol for further details

2.4. Statistical Hypotheses / Statistical Analyses

This study is designed to characterize the pharmacokinetics of DTG and RPV following a single oral dose of DTG/RPV 50 mg/25 mg FDC in healthy, adult Japanese subjects. Also, this study will seek to assess the safety and tolerability of DTG/RPV 50 mg/25 mg FDC in healthy, adult Japanese participants.

No formal statistical hypothesis will be tested.

3. PLANNED ANALYSES

3.1. Final Analyses

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

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

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	• All participants who sign the ICF	• Screen Failures • Protocol Deviations
Enrolled	• All participants who have a Day 1 visit.	• Study Populations

Population	Definition / Criteria	Analyses Evaluated
Safety	• All participants who enrolled in the study and received at least one dose of study drug.	• Study Population • Safety
Pharmacokinetic (PK)	• All participants in the Safety population for whom a PK sample was obtained and had evaluable PK assay results. • A subject with emesis occurring within 10 hours of the dose will not be considered evaluable.	• PK • Data from subjects who vomit within 10 hours of study drug administration will be excluded from PK concentration summary and PK parameter summary but will be included in the listing and flagged. • Excluded subjects will be flagged in footnotes for summary tables.

Refer to Appendix 9 List of Data Displays which details the population used for each display.

4.1. Protocol Deviations

Term	Definition
Study Deviation Rules Document	The document describing study deviations (and associated coding/naming conventions) that may be identified during a study and the frequency of study deviation reviews.
Protocol Deviation (PD)	Any departure from study-specific requirements specified in a protocol. Subsets of protocol deviations are categorized as important or significant.
Important Protocol Deviations	A subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. All-important deviations have a Violation Flag in CTMS and are associated with a Rule Number.

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 freezing the database to ensure all important deviations are captured and categorised on the protocol deviations dataset.
- This dataset will be the basis for the summaries and listings of protocol deviations.

A separate listing of all inclusion/exclusion criteria deviations will also be provided. This listing will be based on data as recorded on the inclusion/exclusion page of the eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions	
Data Displays for Reporting	
Description	**Order in TLF**
DTG/RPV 50mg/25mg FDC	1

5.2. Baseline Definitions

For all endpoints (except as noted in baseline definitions) the baseline value will be the last available assessment prior to time of the dose, unless noted otherwise. If there are multiple assessments collected on the same scheduled time, the average of these assessments will be used.

Parameter	Study Assessments Considered as Baseline			Baseline Used in Data Display
	Screening	Day -1	Day 1 (Pre-Dose)	
Safety				
Labs	X	X		Day -1
Vital Signs	X	X	X	Day 1 (Pre-Dose)

5.2.1. 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 5.2 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.

5.3. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
10.1	Appendix 1: Protocol Deviation Management and Definitions
10.2	Appendix 2: Schedule of Activities
10.3	Appendix 3: Treatment States and Phases
10.4	Appendix 4: Data Display Standards & handling Conventions
10.5	Appendix 5: Derived and Transformed Data
10.6	Appendix 6: Reporting Standards for Missing data
10.7	Appendix 7: Values of Potential Clinical Importance
10.8	Appendix 8: Abbreviations & Trade Marks

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

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

Table 1 provides an overview of the planned study population analyses, with full details of data displays being presented in Appendix 9: List of Data Displays.

Table 1 Overview of Planned Study Population Analyses

Display Type	Data Display's Generated		
	Figure	Table	Listing
Randomisation			
Randomisation			Y
Subject Disposition			
Participant Disposition		Y	
Reasons for Screen Failure		Y	Y
Reasons for Withdrawals			Y
Important Protocol Deviations		Y	Y
Inclusion and Exclusion Criteria Deviations			Y
Subjects Excluded from Analysis Populations			Y
Medical history		Y	
Demography			
Demographics Characteristics		Y	Y
Race and Racial Combinations		Y	Y
Age Ranges		Y	
Concomitant Medications			
Concomitant Medications			Y

7. SAFETY ANALYSES

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

7.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs) and other significant AEs will be based on GSK Core Data Standards. The details of the planned displays are provided in Appendix 9: List of Data Displays.

Table 2 Overview of Planned Safety Analyses

Display Type	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Exposure								
Exposure Data				Y				
Adverse Events								
Relationship Between System Organ Class and Verbatim Term				Y				
Subject Numbers for Individual AEs				Y				
All AEs	Y			Y				
All Drug-Related AEs	Y			Y				
Serious AEs				Y				
Withdrawal AEs				Y				

NOTES :

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

7.2. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Hematology laboratory tests, Urinalysis, and liver function tests will be based on GSK Core Data Standards. The details of the planned displays are in Appendix 9: List of Data Displays.

Display Type	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Laboratory Values								
Clinical Chemistry	Y			Y [1]	Y			
Hematology	Y			Y [1]	Y			
Abnormal Chemistry				Y [1]				
Abnormal Hematology				Y [1]				
Urinalysis	Y			Y [1]				

Electrocardiograms (ECGs)								
ECG Findings	Y			Y [2]				
ECG Values				Y [3]				
Vital Signs								
Vital Signs	Y			Y [3]	Y			
Liver								
Liver Events [1]				Y				

NOTES :
1. Displays contain only participants with DAIDS toxicities for HIV-infected patients
2. Displays contain only participants with abnormal findings
3. Displays contain only participants with values of potential clinical importance

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

7.3. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned displays are presented in Appendix 9: List of Data Displays.

Display Type	**Absolute**				**Change from Baseline**			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Electrocardiograms (ECGs)								
ECG Findings	Y			Y [2]				
ECG Values				Y [3]				
Vital Signs								
Vital Signs	Y			Y [3]	Y			
Liver								
Liver Events [1]				Y				

NOTES :
1. Displays contain only participants with DAIDS toxicities for HIV-infected patients
2. Displays contain only participants with abnormal findings
3. Displays contain only participants with values of potential clinical importance

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

Individual = Represents TFL related to any displays of individual participant observed raw data.

8. PHARMACOKINETIC ANALYSES

8.1. Primary Pharmacokinetic Analyses

8.1.1. Overview of Planned Pharmacokinetic Analyses

The PK analyses will be based on the PK Population, unless otherwise specified.

Table 3 provides an overview of the planned analyses, with full details being presented in Appendix 9: List of Data Displays.

Table 3 Overview of Planned Pharmacokinetic Analyses

Endpoints	Untransformed				Loge-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[3]	Y	Y[3]	Y		Y		

NOTES :

- T = Table, F = Figure, L = Listing, 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.
- Tmax and tlag 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. Individual and Box Plot of DTG and RPV PK Parameters by Treatment

8.1.2. Endpoint / Variables

8.1.2.1. Drug Concentration Measures

Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 10.4.3 Reporting Standards for Pharmacokinetic)

8.1.2.2. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin 6.3 or higher. All calculations of non-compartmental parameters will be based on actual sampling times. Pharmacokinetic parameters listed will be determined from the plasma concentration-time data, as data permits.

Parameter	Parameter Description
AUC(0-t)	Area under the concentration-time curve (AUC) from time 0 (predose) to time of the last quantifiable concentration, to be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
AUC(0-24)	Area under the concentration-time curve (AUC) over time 0 (predose) to 24 hours

Parameter	Parameter Description
	after dose administration, to be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
AUC(0-72)	Area under the concentration-time curve (AUC) over time 0 (predose) to 72 hours after dose administration, to be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
AUC(0-∞)	Area under the concentration-time curve from time 0 (predose) extrapolated to infinite time, calculated as: $AUC(0-\infty) = AUC(0-t) + Ct / \lambda z$ where Ct is the last observed quantifiable concentration.
%AUCex	The percentage of AUC(0-∞) obtained by extrapolation (%AUCex) will be calculated as: $[AUC(0-\infty) – AUC(0-t)] / AUC(0-\infty) \times 100$
Cmax	Maximum observed concentration, determined directly from the concentration-time data.
Ct	The last observed quantifiable concentration
C24	The observed concentration at 24 hours after dose administration
t	time of last quantifiable concentration
Tmax	Time to first occurrence of Cmax
Tlast	Time of last quantifiable concentration
tlag	Lag time before observation of drug concentrations in sampled matrix
t½	Terminal phase half-life will be calculated as: $t½ = \ln 2 / \lambda z$
λz	Terminal-phase rate constant
CL/F	The apparent oral clearance
Vz/F	The apparent volume of distribution during the terminal phase

NOTES:

- Additional parameters may be included as required.

8.1.3. Population of Interest

The primary pharmacokinetic analyses will be based on the "Pharmacokinetic" population, unless otherwise specified.

8.1.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 9: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 8.1.2 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

For each of the Plasma DTG and RPV parameters $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, C_{max}, t_{lag}, t_{max}, t, $t_{½}$, λz, $\%AUC_{ex}$, $AUC_{(0-24)}$, $AUC_{(0-72)}$, CL/F and Vz/F, C_t, and C_{24} , 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.
- **Loge-transformed Data:** Geometric mean, 95% CI for the geometric mean, SD of loge-transformed data and %CVb

For %AUCex, Tmax, tlag, 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 format 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.

9. REFERENCES

GlaxoSmithKline Document Number 2018N392977_00: A Phase I, Open-label, Single-dose Study to Investigate the Pharmacokinetics, Safety and Tolerability of Dolutegravir + Rilpivirine (JULUCA™) 50 mg/25 mg tablets in healthy participants of Japanese descent. Effective Date: 04-APR-2019

10. APPENDICES

10.1. Appendix 1: Protocol Deviation Management and Definitions

Please refer to the Protocol Deviation Management Plan (PDMP).

10.1.1. Exclusions from PK Population

A subject meeting any of the following criteria will be excluded from the PK population:

Number	Exclusion Description
01	A subject with emesis occurring within 10 hours of the dose

10.2. Appendix 2: Schedule of Activities

10.2.1. Protocol Defined Schedule of Events

Procedure	Day -1	Study Intervention Period										Follow-Up (12 - 17 days post last dose) [2,3]	Notes
		Day											
		1			2	3	4	6	8	10	12		
		Pre Dose	0 hr	Post Dose	24 hr	48 hr	~72 hr	~120 hr	~168 hr	~216 hr	~264 hr		
Admission to Unit	X												
Discharge						X							
Outpatient Visit							X	X	X	X	X	X	
Brief Physical Exam[1]	X												
Pregnancy test (urine or serum)	X											X	
Urine/Drug/Alcohol/ Cotinine	X												Illicit Drug/Alcohol/Cotinine performed at the standard practice of the site.
12-Lead ECG	X												Single ECGs will be collected
Vital Signs (VS) measurements	X	X										X	Single VS measurements will be performed at all time points.
Safety lab assessments (Hematology,Chemistry)	X					X							Glucose fasting is required approximately 10 hours prior to dosing on Day -1 and at least 6 hours at Day 3 post dose.
DTG/RPV FDC Dosing			X										Subjects will fast for ~10 hours and receive the dose ~30 minutes (± 5 minutes) after the start of a standardized moderate fat breakfast

Procedure	Day -1	Study Intervention Period										Follow-Up (12 - 17 days post last dose) [2,3]	Notes
		Day											
		1			2	3	4	6	8	10	12		
		Pre Dose	0 hr	Post Dose	24 hr	48 hr	~72 hr	~120 hr	~168 hr	~216 hr	~264 hr		
Pharmacokinetic Sampling		X		Collected at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 12, 16, 24, and 48 hours post-dose			X	X	X	X	X		Subjects should be scheduled to provide PK samples in the morning on Days 4, 6, 8, 10, and 12; Days 8, 10, and 12 are for RPV sampling only. The 4-hour post-dose sample must be drawn prior to the subjects' first post-dose meal
SAE Review	X	←==========X==========→										X	
AE Review		←==========X==========→										X	
Concomitant medication review	X	←==========X==========→										X	

10.3. Appendix 3: Study Phases

10.3.1. Study Phases

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

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

1. **NOTES:**

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

10.3.2. Study Phases for AE Data

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

Study Phase	Definition
Pre-Treatment	Event Start Date < Initial Study Treatment Date
On-Treatment	If event onset date is on or after the initial treatment date & on or before the final treatment date with 3 days lag time. Initial Study Treatment Date ≤ Event Start Date ≤ Final Study Treatment Date + 3 days
Post-Treatment	If event onset date is after the final treatment date with 3 days lag time. Event Start Date > Final Study Treatment Date + 3 days
Onset Time Since 1st Dose (Days)	If Treatment Date > Event Onset Date = Event Onset Date – Treatment Date If Treatment Date ≤ Event Onset Date = Event Onset Date – Treatment Date+1 Missing otherwise.
Duration (Days)	Event Resolution Date – Event Onset Date + 1
Drug-related	If relationship is marked 'YES' on eCRF OR value is missing.

NOTES:

- If the initial and final study treatment dates are missing then the event will be considered to be On-Treatment.

10.4. Appendix 4: Data Display Standards & Handling Conventions

10.4.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: US1SALX00259-HARP PROD-US
HARP Compound	: GSK3365791
Analysis Datasets	
Analysis datasets will be created according to Clinical Data Interchange Standards Consortium (CDISC) standards (SDTM IG Version 3.2 & Analysis Data Model (ADaM) Implementation Guide (ADaM IG) Version 1.0 or higher dataset standards)	
Generation of RTF Files	
• RTF files will be generated for summary displays.	

10.4.2. Reporting Standards

General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics

Formats
• 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, unless otherwise stated. • Numeric data will be reported at the precision collected on the eCRF. • 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:
  • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  • 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:
  • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  • Unscheduled or unplanned readings will be presented within the subject's listings.

Unscheduled Visits
• Unscheduled visits will not be included in summary tables and/or 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, %
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

10.4.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	
PC Windows Non-Linear (WNL) File	PC WNL file (CSV format) for the non-compartmental analysis by Clinical Pharmacology Modelling and Simulation function will be created according to [Insert document name]. Note: Concentration values will be imputed as per GUI_51487
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1. Note: Concentration values will be imputed as per GUI_51487 for descriptive summary statistics/analysis and summarized graphical displays only.
Pharmacokinetic Parameter Derivation	
PK Parameter to be Derived by CPMS	The following PK parameters will be derived by the CPMS: Plasma DTG and RPV $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, C_{max}, t_{lag}, t_{max}, t, $t_{½}$, λz, $\%AUC_{ex}$, $AUC_{(0-24)}$, $AUC_{(0-72)}$, CL/F and Vz/F, C_t, and C_{24}
Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	Refer to [Standards for Handling NQ Impacted PK Parameters].
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1.

10.5. Appendix 5: Derived and Transformed Data

10.5.1. General

Multiple Measurements at One Analysis 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. • Participants having both High and Low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

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

10.5.2. Study Population

Age
• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows: ○ Only the year of birth will be collected. The date and month will be imputed as '30th June'. • Birth date will be presented in listings as 'YYYY'.
Body Mass Index (BMI)
• Calculated as **Weight (kg) / [Height (m)^2]**

10.5.3. Safety

Adverse Events
AE'S of Special Interest
• No analysis for AEs of Special Interest will be performed.

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: $$RR = \left[\left(\frac{QT}{QTcB}\right)^2\right] * 1000$$ [2] If QTcF is machine read and QTcB is not provided, then: $$RR = \left[\left(\frac{QT}{QTcF}\right)^3\right] * 1000$$ • If ECGs are manually read, the RR value preceding the measurement QT interval should be a

ECG Parameters
collected value THEN do not derive. • Machine read values of RR should not be replaced with derived values.
Corrected QT Intervals
• When not entered directly in the eCRF, corrected QT intervals by 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: $QTcB = \frac{QT}{\sqrt{\frac{RR}{1000}}}$ $QTcF = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$

10.6. Appendix 6: Reporting Standards for Missing Data

10.6.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as if he/she has completed all phases of the study including the last visit or the last scheduled procedure as shown in the Schedule of Activities. • Withdrawn subjects were not replaced in the study. • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

10.6.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: ○ These data will be indicated by the use of a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. ○ Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.
Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

10.6.2.1. Handling of Missing Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: ○ Missing Start Day: First of the month will be used unless this is before the start date of study treatment; in this case the study treatment start date will be used and hence the event is considered On-treatment as per Appendix 4: Study Phases and Treatment Emergent Adverse Events. ○ Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.

10.6.2.2. Handling of Partial Dates

Element	Reporting Detail
Concomitant Medications	• Partial dates for any concomitant medications recorded in the eCRF will be imputed using the following convention:

	• If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month • If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. • The recorded partial date will be displayed in listings.
AEs	• Any partial dates for AEs will be raised to data management. If the full date cannot be ascertained, the following assumptions will be made: o If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month. o However, if these results in a date prior to Week 1 Day 1 and the event could possibly have occurred during treatment from the partial information, then the Week 1 Day 1 date will be assumed to be the start date. o The AE will then be considered to start on-treatment (worst case). o If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. • The recorded partial date will be displayed in listings.

10.7. Appendix 7: Values of Potential Clinical Importance

10.7.1. Laboratory Values

10.7.2. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute			
Absolute QTc Interval	msec		> 450[1]
Absolute PR Interval	msec	< 110[1]	> 220[1]
Absolute QRS Interval	msec	< 75[1]	> 110[1]

NOTES:

1. Represent standard ECG values of PCI for HIV studies.

10.7.3. Vital Signs

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	Upper
Systolic Blood Pressure	mmHg	< 85	> 160
Diastolic Blood Pressure	mmHg	< 45	> 100
Heart Rate	bpm	< 40	> 110

10.8. Appendix 8: Abbreviations & Trade Marks

10.8.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
ADaM IG	Analysis Data Model Implementation Guide
AE	Adverse Event
AUC	Area under the concentration-time curve
AUC(0-t)	Area under the concentration-time curve from time 0 (predose) to time of the last quantifiable concentration
AUC(0-24)	Area under the concentration-time curve over time 0 (predose) to 24 hours after dose administration
AUC(0-72)	Area under the concentration-time curve over time 0 (predose) to 72 hours after dose administration
AUC(0-∞)	Area under the concentration-time curve from time 0 (predose) extrapolated to infinite time
%AUCex	The percentage of AUC(0-∞) obtained by extrapolation
BMI	Body Mass Index
C24	The observed concentration at 24 hours after dose administration
CDISC	Clinical Data Interchange Standards Consortium
CL/F	The apparent oral clearance
Cmax	Maximum observed concentration
CI	Confidence Interval
Ct	The last observed quantifiable concentration
CTMS	Clinical Trial Management System
CV	Coefficient of variation
CV_b	Coefficient of variation (Between)
DAIDS	Division of Acquired Immune Deficiency Syndrome
DTG	Dolutegravir
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
GSK	GlaxoSmithKline
ICH	International Conference on Harmonisation
IDSL	Integrated Data Standards Library
kg	Kilograms
m	Meters
mg	Milligrams
msec	Milliseconds
PK	Pharmacokinetic
QTcF	Fridericia's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
R&D	Research and Development
RAP	Reporting & Analysis Plan
RPV	Rilpivirine
SAC	Statistical Analysis Complete

Abbreviation	Description
SAS	Statistical Analysis Software
SD	Standard deviation
SDTM	Study Data Tabulation Model
t	Time of last quantifiable concentration
TFL	Tables, Figures & Listings
t½	Terminal phase half-life
tlag	Lag time before observation of drug concentrations in sampled matrix
Tlast	Time of last quantifiable concentration
Tmax	Time to first occurrence of Cmax
Vz/F	The apparent volume of distribution during the terminal phase
λz	terminal phase rate constant

10.8.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
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10.9. Appendix 9: List of Data Displays

10.9.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.7	N/A
Safety	3.1 to 3.13	N/A
Pharmacokinetic	4.1 to 4.6	4.1 to 4.10
Section	**Listings**	
ICH Listings	1 to 29	
Other Listings	30 to 33	

10.9.2. Deliverables

Delivery [Priority] [1]	Description
SAC [1]	Final Statistical Analysis Complete

NOTES:
1. Indicates priority (i.e. order) in which displays will be generated for the reporting effort

10.9.3. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	Safety	ES1	Summary of Participant Disposition for the Participant Conclusion Record		SAC [1]
1.2.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure		SAC [1]
1.3.	Screened	DV1	Summary of Important Protocol Deviations		SAC [1]
1.4.	Safety	DM1	Summary of Demographic Characteristics		SAC [1]
1.5.	Enrolled	DM11	Summary of Age Ranges		SAC [1]
1.6.	Safety	DM5	Summary of Race and Racial Combinations		SAC [1]
Prior and Concomitant Medications					
1.7.	Safety	MH1 / MH4	Summary of Current Medical Conditions		SAC [1]

10.9.4. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
3.1.	Safety	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term		SAC [1]
3.2.	Safety	AE1	Summary All Drug-Related Adverse Events		SAC [1]
3.3.	Safety	AE5a	Summary of Adverse Events by Maximum Grade by System Organ Class and Preferred Term		SAC [1]
Laboratory: Chemistry					
3.4.	Safety	LB1	Summary of Chemistry Values		SAC [1]
3.5.	Safety	LB1	Summary of Chemistry Changes from Baseline	Add Footnote - Note: Baseline is defined as Day -1	SAC [1]
3.6.	Safety	LB16	Summary of Chemistry Results by Maximum Grade Increase Post-Baseline Relative to Baseline		SAC [1]
Laboratory: Hematology					
3.7.	Safety	LB1	Summary of Hematology Values		SAC [1]
3.8.	Safety	LB1	Summary of Hematology Changes from Baseline	Add Footnote - Note: Baseline is defined as Day -1	SAC [1]
3.9.	Safety	LB16	Summary of Hematology Results by Maximum Grade Increase Post-Baseline Relative to Baseline		SAC [1]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory: Urinalysis					
3.10.	Safety	LB1	Summary of Urinalysis Dipstick Results		SAC [1]
Laboratory: ECG					
3.11.	Safety	EG1	Summary of ECG Findings		SAC [1]
Vital Signs					
3.12.	Safety	VS1	Summary of Vital Signs		SAC [1]
3.13.	Safety	VS1	Summary of Change from Baseline in Vital Signs	Add Footnote - Note: Baseline is defined as Day 1 (Predose)	SAC [1]

10.9.5. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentration Data					
4.1.	PK	PKCT1	Summary of DTG Plasma Pharmacokinetic Concentration-Time Data by Treatment		SAC [1]
4.2.	PK	PKCT1	Summary of RPV Plasma Pharmacokinetic Concentration-Time Data by Treatment		SAC [1]
PK Derived Parameters					
4.3.	PK	PKPT1	Summary of Derived DTG Plasma Pharmacokinetic Parameters (Non-Transformed) by Treatment	Parameters with units	SAC [1]
4.4.	PK	PKPT3	Summary of Derived DTG Plasma Pharmacokinetic Parameters (Loge-transformed) by Treatment	Parameters with units	SAC [1]
4.5.	PK	PKPT1	Summary of Derived RPV Plasma Pharmacokinetic Parameters (Non-Transformed) by Treatment	Parameters with units	SAC [1]
4.6.	PK	PKPT3	Summary of Derived RPV Plasma Pharmacokinetic Parameters (Loge-transformed) by Treatment	Parameters with units	SAC [1]

10.9.6. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Individual Concentration Plots					
4.1.	PK	PKCF1	Individual participant DTG Plasma Concentration-Time Plots by Participant (Linear and Semi-Logarithmic)	Paginate by Participant	SAC [1]
4.2.	PK	PKCF1	Individual participant RPV Plasma Concentration-Time Plots by Participant (Linear and Semi-Logarithmic)	Paginate by Participant	SAC [1]
4.3.	PK	PKCF6	Individual participant DTG Plasma Concentration-Time Plots by treatment (Linear and Semi-Logarithmic)	Only 1 page as one Treatment group	SAC [1]
4.4.	PK	PKCF6	Individual participant RPV Plasma Concentration-Time Plots by treatment (Linear and Semi-Logarithmic)	Only 1 page as one Treatment group	SAC [1]
Mean / Median Concentration Plots					
4.5.	PK	PKCF2	Arithmetic Mean DTG Plasma Concentration-time Plot (Linear and Semi-log)	Use nominal times in X Axis,	SAC [1]
4.6.	PK	PKCF2	Arithmetic Mean RPV Plasma Concentration-time Plot (Linear and Semi-log)	Use nominal times in X Axis,	SAC [1]
4.7.	PK	PKCF3	Median DTG Plasma Concentration-time Plot (Linear and Semi-log)	Use nominal times in X Axis,	SAC [1]
4.8.	PK	PKCF3	Median RPV Plasma Concentration-time Plot (Linear and Semi-log)	Use nominal times in X Axis,	SAC [1]

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Derived Parameters					
4.9	PK	Figure 3.19 201674	Individual and Box Plot of DTG PK Parameters by Treatment	AUC(0-∞), AUC(0-24), AUC(0-72), AUC(0-t), %AUCex, CL/F, C24, Cmax, t½, tlag, tlast, tmax, Vz/F	SAC [1]
4.10	PK	Figure 3.19 201674	Individual and Box Plot of RPV PK Parameters by Treatment	AUC(0-∞), AUC(0-24), AUC(0-72), AUC(0-t), %AUCex, CL/F, C24, Cmax, t½, tlag, tlast, tmax, Vz/F	SAC [1]

10.9.7. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	Screened	ES7	Listing of Reasons for Screen Failure		SAC [1]
2.	Safety	ES2	Listing of Reasons for Study Withdrawal		SAC [1]
3.	Safety	TA1 / CP_RD1x	Listing of Planned and Actual Treatments		SAC [1]
Protocol Deviations					
4.	Safety	DV2	Listing of Important Protocol Deviations		SAC [1]
5.	Safety	IE4	Listing of Participants with Inclusion/Exclusion Criteria Deviations		SAC [1]
Populations Analysed					
6.	Screening	SP3	Listing of Participants Excluded from Any Population		SAC [1]
Demography					
7.	Safety	DM4	Listing of Demographic Characteristics		SAC [1]
8.	Safety	DM10	Listing of Race		SAC [1]
Prior and Concomitant Medications					
9.	Safety	CP_CM4	Listing of Concomitant Medications		SAC [1]
Exposure					
10.	Safety	EX34	Listing of Exposure Data		SAC [1]
Adverse Events					
11.	Safety	CP_AE9	Listing of All Adverse Events		SAC [1]
12.	Safety	CP_AE9	Listing of Drug Related Adverse Events		SAC [1]

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
13.	Safety	AE8	Listing of Non-Serious Adverse Events		SAC [1]
14.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events		SAC [1]
15.	Safety	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text		SAC [1]
Serious and Other Significant Adverse Events					
16.	Safety	CP_AE9	Listing of Adverse Events Leading to Withdrawal from study		SAC [1]
17.	Safety	CP_AE9a	Listing of Serious Adverse Events		SAC [1]
All Laboratory					
18.	Safety	LB6	Listing of Clinical Chemistry Toxicities of all Lab Abnormalities		SAC [1]
19.	Safety	LB6	Listing of All Clinical Chemistry Data for Participants with Lab Abnormalities		SAC [1]
20.	Safety	LB6	Listing of Hematology Toxicities of all Lab Abnormalities		SAC [1]
21.	Safety	LB6	Listing of All Hematology Data for Participants with Lab Abnormalities		SAC [1]
22.	Safety	LB6	Listing of Urinalysis Data for Subjects with Positive Dipstick or Microscopic Results		SAC [1]
ECG					
23.	Safety	EG4	Listing of All ECG Values for Participants with Any Value of Potential Clinical Importance		SAC [1]
24.			Listing of ECG Values of Potential Clinical Importance		
25.	Safety	EG6	Listing of All ECG Findings for Participants with an Abnormal ECG Finding		SAC [1]
26.	Safety	EG6	Listing of Abnormal ECG Findings		SAC [1]
Vital Signs					

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
27.	Safety	VS5	Listing of All Vital Signs Data for Participants with Any Value of Potential Clinical Importance		SAC [1]
28.	Safety	VS5	Listing of Vital Signs of Potential Clinical Importance		
Liver Events					
29.	Safety	LIVER5	Listing of Liver Monitoring/Stopping Event Reporting		SAC[1]

10.9.8. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK					
30.	PK	PKCL1X	Listing of DTG Plasma Pharmacokinetic Concentration-Time Data		SAC [1]
31.	PK	PKCL1X	Listing of RPV Plasma Pharmacokinetic Concentration-Time Data		SAC [1]
32.	PK	PKPL1X	Listing of Derived DTG Plasma PK Parameters		SAC [1]
33.	PK	PKPL1X	Listing of Derived RPV Plasma PK Parameters		SAC [1]