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

Title	:	A 2-Part, Phase I, Single-Dose, 3-Period Crossover Relative Bioavailability Study of a Pediatric TRIUMEQ Dispersible Tablet and Pediatric Dolutegravir and Lamivudine (DTG/3TC) Fixed Dose Combination Dispersible Tablet Formulations as Compared With Adult Tablets in Healthy Volunteers
Compound Number	:	GSK1349572+GR109714+GI265235 (GSK2619619) and GSK1349572+GR109714 (GSK3515864)
Effective Date	:	25-APR-2018

Description :

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 205894.
- This RAP is intended to describe the safety, tolerability, and pharmacokinetic (PK) analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

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1. REPORTING & ANALYSIS PLAN SYNOPSIS

Overview	Key Elements of the RAP
Purpose	• The purpose of this reporting and analysis plan (RAP) is to describe any planned analyses and output to be included in the clinical study report for Protocol 205894.
Protocol	• This RAP is based on the original protocol (Dated: 18/JAN/2018) of study 205894 (GlaxoSmithKline Document Number. 2017N330422_00).
Primary Objective	• Part 1: • To compare the relative bioavailability (BA) of dolutegravir (DTG), abacavir (ABC), and lamivudine (3TC) administered as pediatric TRIUMEQ dispersible tablets with the conventional adult TRIUMEQ tablet (reference) administered as direct-to-mouth when: • Pediatric TRIUMEQ dispersible tablets are administered as a dispersion and taken immediately • Pediatric TRIUMEQ dispersible tablets are administered as direct to-mouth. • Part 2: • To compare the relative BA of DTG and 3TC administered as pediatric DTG/3TC dispersible tablets with the conventional adult DTG and 3TC tablets (reference) administered as direct-to-mouth when: • Pediatric DTG/3TC dispersible tablets are administered as a dispersion and taken immediately • Pediatric DTG/3TC dispersible tablets are administered as direct-to-mouth
Primary Endpoint	• Parts 1 and 2: • Plasma DTG, ABC (Part 1 only), and 3TC: • Area under the plasma concentration-time curve (AUC) from time of dose extrapolated to infinite [AUC(0-∞)], AUC from time of dose to last measurable concentration [AUC(0-t)], and maximum observed concentration (Cmax).
Secondary Objectives	• Part 1: • To compare the single-dose pharmacokinetics (PK) of DTG, ABC, and 3TC administered as pediatric TRIUMEQ dispersible tablets with the conventional adult TRIUMEQ tablets (reference) administered as direct-to-mouth when: • Pediatric TRIUMEQ dispersible tablets are administered as a dispersion and taken immediately • Pediatric TRIUMEQ dispersible tablets are administered as direct to-mouth • To evaluate the safety and tolerability of DTG, ABC, and 3TC administered as pediatric TRIUMEQ dispersible tablets as compared with conventional adult TRIUMEQ tablet (reference) administered as direct-to-mouth

Overview	Key Elements of the RAP
	• Part 2: • To compare the single-dose PK of DTG and 3TC administered as pediatric DTG/3TC dispersible tablets, with the conventional adult DTG and 3TC tablets (reference) administered as direct-to-mouth when: • Pediatric DTG/3TC dispersible tablets are administered as a dispersion and taken immediately • Pediatric DTG/3TC dispersible tablets are administered as direct to-mouth • To evaluate the safety and tolerability of DTG and 3TC administered as pediatric DTG/3TC dispersible tablets as compared with the conventional adult DTG and 3TC tablets (reference) administered as direct-to-mouth
Secondary Endpoints	• Parts 1 and 2: • Plasma DTG, ABC (Part 1 only) and 3TC: • AUC from time of dose to 24 hours [AUC(0-24)], time to maximum concentration (Tmax), time of last quantifiable concentration (Tlast), apparent oral clearance (CL/F), apparent volume of distribution (VZ/F), observed concentration at 24 hours postdose (C24), last observed quantifiable concentration (Ct), and terminal elimination phase half-life (t½), • Plasma DTG: lag time for absorption (tlag) • Safety and tolerability parameters for adverse events (AEs)/serious adverse events (SAE), observed and change from baseline clinical laboratory assessments, electrocardiogram (ECG), and vital signs
Exploratory Objective	• Parts 1 and 2: • To evaluate the palatability of the dispersible tablets
Exploratory Endpoint	• Parts 1 and 2: • Palatability questionnaire
Study Design	• This study will be conducted as a 2-part, open-label, single-dose, 3-period, randomized, crossover study to compare the relative BA of pediatric TRIUMEQ dispersible tablets with an adult TRIUMEQ conventional tablet formulation (Part 1) and of pediatric DTG/3TC dispersible tablets with adult DTG and 3TC conventional tablets formulation (Part 2) in healthy volunteers under fasted conditions. Prior to dosing on Day 1 of Period 1 in each part, participants will be randomized to 1 of 6 treatment sequences (ABC, BCA, CAB, ACB, BAC, or CBA in Part 1; DEF, EFD, FDE, DFE, EDF, or FED in Part 2) and will receive a single dose of each of the 3 treatments administered as 1 treatment per period. Parts 1 and 2 of the study are independent of one another and may be run in parallel. • Treatments are defined below:

Overview	Key Elements of the RAP
	• Part 1 ○ Treatment A: Adult TRIUMEQ (DTG 50 mg/ABC 600 mg/3TC 300 mg, 1 conventional tablet) administered as direct-to-mouth (reference) ○ Treatment B: Pediatric TRIUMEQ (DTG 5 mg/ABC 60 mg/3TC 30 mg, 10 dispersible tablets) administered as a dispersion and taken immediately (test) ○ Treatment C: Pediatric TRIUMEQ (DTG 5 mg/ABC 60 mg/3TC 30 mg, 10 dispersible tablets) administered as direct-to-mouth (test). • Part 2 ○ Treatment D: Adult DTG (50 mg, 1 conventional tablet) and adult 3TC (300 mg, 1 conventional tablet) administered as direct-to-mouth (reference) ○ Treatment E: Pediatric DTG/3TC (DTG 5 mg/3TC 30 mg, 10 dispersible tablets) administered as a dispersion and taken immediately (test) ○ Treatment F: Pediatric DTG/3TC (DTG 5 mg/3TC 30 mg, 10 dispersible tablets) administered as direct-to-mouth (test)
Planned Analyses	• Plasma DTG, ABC (Part 1 only), and 3TC concentration-time data will be analyzed by non-compartmental methods with Phoenix WinNonlin Version 6.4 or higher. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following PK parameters will be determined, as data permit: Cmax, Tmax, Tlast, AUC(0-t), AUC24, AUC(0-∞), t1/2, tlag (DTG only), C24, Ct, Vz/F, and CL/F. • Pharmacokinetic data for each part 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. • The primary PK parameters for DTG, ABC (Part 1 only), and 3TC in Part 1 (AUC[0-∞], AUC[0-t], and Cmax) will be $\log_e$-transformed and separately analyzed using a mixed effects model with fixed-effect terms for Period, Treatment, and Treatment Sequence for each treatment comparison. Participant will be nested within Treatment Sequence and treated as a random effect in the model. Point estimates and their associated 90% CIs will be constructed for the differences in PK parameter values between test and reference treatments. 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 from test and reference treatments. • Safety data for each part 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. • Palatability questionnaire variables for each part will be summarized descriptively.
Analysis Populations	• All Participants Population: all participants who receive at least 1 dose of study medication. This population will be used for all demographic and safety

Overview	Key Elements of the RAP
	summaries • PK Population: participants in the 'All Participants' population for whom a PK sample was obtained and who had evaluable PK assay results. PK samples that may be affected by protocol deviations will be reviewed by the study team to determine whether or not the sample will be excluded. This population will be used for reporting of PK data.
Hypothesis	This study is designed to estimate the relative BA of each test treatment to the reference treatment (B vs. A, C vs. A in Part 1; E vs. D, F vs. D in Part 2) in the fasted state. • No formal hypothesis will be tested. For each primary pharmacokinetic endpoint (AUC[0-∞], AUC[0-t], and Cmax), point estimates and corresponding 90% CIs will be constructed for the ratio of the geometric mean of the test treatment to the geometric mean of the reference treatment, μ(test)/μ(reference).

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

An additional comparison between the two administration approaches of Pediatric TRIUMEQ in Part 1 and Pediatric DTG/3TC in Part 2, direct to mouth and dispersion (B vs. C, and E vs. F) will be included within the primary statistical analyses. The secondary PK parameter C24 will be included in the primary statistical analysis described in Section 7.1.3.2 of this document.

Screened and Enrolled populations have been defined as additional analysis populations.

There have been no other changes to the protocol defined statistical analysis plan.

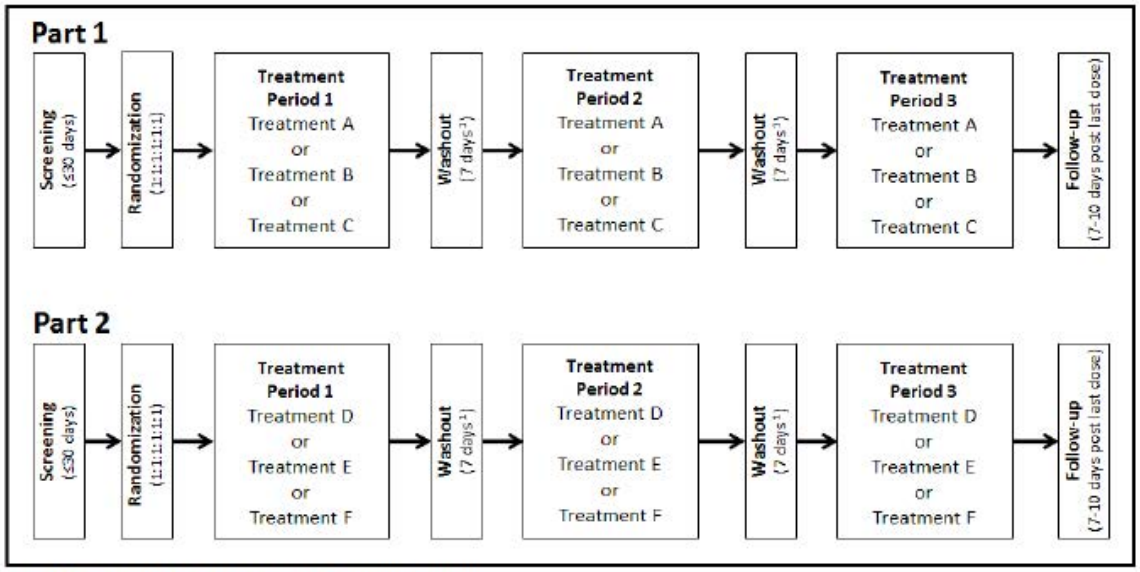
2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
Part 1 • To compare the relative BA of DTG, ABC, and 3TC administered as pediatric TRIUMEQ dispersible tablets with the conventional adult TRIUMEQ tablet (reference) administered as direct-to-mouth when: o Pediatric TRIUMEQ dispersible tablets are administered as a dispersion and taken immediately o Pediatric TRIUMEQ dispersible tablets are administered as direct to-mouth	**Part 1** • Plasma DTG, ABC, and 3TC: AUC(0-∞), AUC(0-t), and Cmax.
Part 2 • To compare the relative BA of DTG and 3TC administered as pediatric DTG/3TC dispersible tablets with the conventional adult DTG and 3TC tablets (reference) administered as direct-to-mouth when: o Pediatric DTG/3TC dispersible tablets are administered as a dispersion and taken immediately o Pediatric DTG/3TC dispersible tablets are administered as direct-to-mouth	**Part 2** • Plasma DTG and 3TC: AUC(0-∞), AUC(0-t), and Cmax.

Objectives	Endpoints
Secondary Objectives	**Secondary Endpoints**
Part 1 • To compare the single-dose pharmacokinetics (PK) of DTG, ABC, and 3TC administered as pediatric TRIUMEQ dispersible tablets with the conventional adult TRIUMEQ tablets (reference) administered as direct-to-mouth when: o Pediatric TRIUMEQ dispersible tablets are administered as a dispersion and taken immediately o Pediatric TRIUMEQ dispersible tablets are administered as direct to-mouth • To evaluate the safety and tolerability of DTG, ABC, and 3TC administered as pediatric TRIUMEQ dispersible tablets as compared with conventional adult TRIUMEQ tablet (reference) administered as direct-to-mouth.	**Part 1** • Plasma DTG, ABC, and 3TC: AUC(0-24), Tmax, Tlast, CL/F, Vz/F, C24, Ct, t½ • Plasma DTG: tlag • Safety and tolerability parameters for AEs/ SAEs, observed and change from baseline clinical laboratory assessments, ECG, and vital signs.
Part 2 • To compare the single-dose pharmacokinetics (PK) of DTG and 3TC administered as pediatric DTG/3TC dispersible tablets, with the conventional adult DTG and 3TC tablets (reference) administered as direct-to-mouth when: o Pediatric DTG/3TC dispersible tablets are administered as a dispersion and taken immediately o Pediatric DTG/3TC dispersible tablets are administered as direct to-mouth • To evaluate the safety and tolerability of DTG and 3TC administered as pediatric DTG/3TC dispersible tablets as compared with the conventional adult DTG and 3TC tablets (reference) administered as direct-to-mouth	**Part 2** • Plasma DTG and 3TC: AUC(0-24), Tmax, Tlast, CL/F, Vz/F, C24, Ct, t½ • Plasma DTG: tlag • Safety and tolerability parameters for AEs/ SAEs, observed and change from baseline clinical laboratory assessments, ECG, and vital signs.
Exploratory Objectives	**Exploratory Endpoints**
Parts 1 and 2 • To evaluate the palatability of the dispersible tablets.	**Parts 1 and 2** • Palatability questionnaire.

2.3. Study Design

Overview of Study Design and Key Features



1. Washout will be at least 7 days minus 4 hours.

Design Features	• Phase I, 2-part, open-label, randomized, 3-period, cross-over study. • **Part 1**: Approximately 18 participants in a 3-period, cross-over study that will compare the relative BA of pediatric TRIUMEQ administered as a dispersion and taken immediately (Treatment B) or administered as direct-to-mouth (Treatment C) with adult TRIUMEQ administered direct-to-mouth (Treatment A). Each participant will receive all three treatments according to their assignment to one of the 6 treatment sequences (ABC, BCA, CAB, ACB, BAC, CBA). Each treatment sequence will be assigned to 3 participants. • **Part 2**: Approximately 18 participants in a 3-period, cross-over study that will compare the relative BA of pediatric DTG/3TC administered as a dispersion and taken immediately (Treatment E) or administered as direct-to-mouth (Treatment F) with adult DTG and adult 3TC administered direct-to-mouth (Treatment D). Each participant will receive all three treatments according to their assignment to one of the 6 treatment sequences (DEF, EFD, FDE, DFE, EDF, FED). Each treatment sequence will be assigned to 3 participants.
Dosing	**Part 1:** • Treatment A: Adult TRIUMEQ (DTG 50 mg/ABC 600 mg/3TC 300 mg, 1 conventional tablet) administered as direct-to-mouth (reference). • Treatment B: Pediatric TRIUMEQ (DTG 5 mg/ABC 60 mg/3TC 30 mg, 10 dispersible tablets) administered as a dispersion and taken immediately (test). • Treatment C: Pediatric TRIUMEQ (DTG 5 mg/ABC 60 mg/3TC 30 mg, 10 dispersible tablets) administered as direct-to-mouth (test).

Overview of Study Design and Key Features	
	Part 2: • Treatment D: Adult DTG (50 mg, 1 conventional tablet) and adult 3TC (300 mg, 1 conventional tablet) administered as direct-to-mouth (reference) • Treatment E: Pediatric DTG/3TC (DTG 5 mg/3TC 30 mg, 10 dispersible tablets) administered as a dispersion and taken immediately (test). • Treatment F: Pediatric DTG/3TC (DTG 5 mg/3TC 30 mg, 10 dispersible tablets) administered as direct-to-mouth (test).
Treatment Assignment	**Part 1:** • On Period 1 Day 1, participants will be randomized to 1 of the 6 following treatment sequences: ABC, BCA, CAB, ACB, BAC, or CBA in accordance with the randomization schedule generated prior to the start of the study, using validated software. **Part 2:** • On Period 1 Day 1, participants will be randomized to 1 of the 6 following treatment sequences: DEF, EFD, FDE, DFE, EDF, or FED in accordance with the randomization schedule generated prior to the start of the study, using validated software.
Interim Analysis	• There will be no interim analysis.

2.4. Statistical Hypotheses

This study is designed to estimate the relative BA of each test treatment to the reference treatment (B vs. A, C vs. A; E vs. D, F vs. D) in both study parts in the fasted state. Administration by either direct to mouth or dispersion will also be directly compared (B vs. C, and E vs. F) in both study parts.

No formal hypothesis will be tested. For each primary pharmacokinetic endpoint (AUC[0-∞], AUC[0-t], and Cmax), point estimates and corresponding 90% CIs will be constructed for the ratio of the geometric mean of the test treatment to the geometric mean of the reference treatment, μ(test)/μ(reference).

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 and database freeze has been declared by Data Management.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	• All participants who signed an informed consent form.	• Screen Failures • Protocol Deviations
Enrolled	• All participants who were randomized	• Study Populations
All Participants	• All participants who receive at least one dose of study medication. This population corresponds to all participants enrolled.	• Demographic • Safety • Exploratory
PK	• Participants in the "All Participants" population for whom a PK sample was obtained and who had evaluable PK assay results. PK samples that may be affected by protocol deviations will be reviewed by the study team to determine whether or not the sample will be excluded.	• PK

NOTES :

- Please refer to Appendix 10: List of Data Displays which details the population to be used for each display being generated.

4.1. Protocol Deviations

- Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.
- 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 and deviations which may lead to exclusion from the analysis 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 summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the electronic case report form (eCRF).

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: Time & Events
10.2	Appendix 2: Treatment States and Phases
10.3	Appendix 3: Data Display Standards & Handling Conventions
10.4	Appendix 4: Derived and Transformed Data
10.5	Appendix 5: Premature Withdrawals & Handling of Missing Data
10.6	Appendix 6: Values of Potential Clinical Importance
10.7	Appendix 7: Multiple Comparisons and Multiplicity
10.8	Appendix 8: Model Checking and Diagnostics for Statistical Analyses.
10.9	Appendix 9: Abbreviations and Trade Marks
10.10	Appendix 10: List of Data Displays
10.11	Appendix 11: 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 "All Participants" 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 10: List of Data Displays.

Table 2 Overview of Planned Study Population Analyses

Display Type	Data Display's Generated		
	Figure	Table	Listing
Enrollment			
Number of Participants Enrolled by Country and Site ID		Y	
Randomisation			
Randomisation			Y
Participant Disposition			
Participant Disposition		Y	
Reasons for Screen Failures		Y	Y
Reasons for Withdrawals			Y
Important Protocol Deviations		Y	Y
Inclusion and Exclusion Criteria Deviations			Y
Demography			
Demographics Characteristics		Y	Y
Race and Racial Combinations		Y	Y
Age Ranges		Y	
Study Populations			Y [1]
Concomitant Medications			
Concomitant Medications			Y

NOTES:

- Y = Yes display generated.

1. Listing includes only participants excluded from any population.

7. PRIMARY STATISTICAL ANALYSES

7.1. Pharmacokinetic Analyses

7.1.1. 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 10: List of Data Displays.

Table 3 Overview of Planned Pharmacokinetic Analyses

Display Type	Untransformed							Ln-Transformed						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
PK Concentrations				Y	Y[1] [2]	Y[1]	Y							
Plasma PK Parameters	Y			Y	Y[1] [2]	Y	Y			Y	Y			

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- 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 participant observed raw data.

1. [1] Linear and Semi-Logarithmic plots will be created on the same display.
2. [2] Separate mean and median plots will be generated.

7.1.2. Drug Concentration Measures

Refer to Appendix 3: Data Display Standards & Handling Conventions (Section 10.3.3 Reporting Process & Standards).

7.1.3. Pharmacokinetic Parameters

7.1.3.1. Deriving Pharmacokinetic Parameters

- Refer to Appendix 3: Data Display Standards & Handling Conventions (Section 10.3.3 Reporting Process & Standards).
- The PK parameters will be calculated by standard non-compartmental analysis according to current working practices and using Phoenix WinNonlin Version 6.4 or higher.
- All calculations of non-compartmental parameters will be based on actual sampling times.
- Pharmacokinetic parameters described in Table 4 will be determined from the plasma concentration-time data, as data permits.

Table 4 Derived Plasma Pharmacokinetic Parameters

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 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: $AUC(0\text{-}\infty) = AUC(0\text{-}t) + Ct / \lambda z$ where Ct is the last observed quantifiable concentration.
%AUCex	The percentage of AUC(0-∞) obtained by extrapolation (%AUCex) will be calculated as: $[AUC(0\text{-}\infty) - AUC(0\text{-}t)] / AUC(0\text{-}\infty) \times 100$
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
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.
- tlag will be calculated for DTG only

7.1.3.2. Statistical Analysis of Pharmacokinetic Parameters

The following PK statistical analyses will only be performed, if sufficient data are available (i.e. if participants have well defined plasma profiles).

Pharmacokinetic Statistical Analyses
Endpoint(s)
• Plasma primary PK endpoints include AUC(0-∞), AUC(0-t) and Cmax and the secondary endpoint C24 for DTG, ABC (only for Part 1), and 3TC, as data permit
Model Specification
• In Part 1 of this study, the ln-transformed AUC(0-∞), AUC(0-t), Cmax, and C24 values for DTG, ABC, and 3TC will be analyzed separately using a mixed effects model, fitting fixed effect terms for period, treatment, and treatment sequence; and treating participant within treatment sequence as a random effect. Point estimates and 90% CIs will be constructed using the residual variance for the following differences of interest: ○ 10 dispersible pediatric TRIUMEQ tablets [DTG 5 mg/ABC 60 mg/3TC 30 mg] administered as a dispersion and taken immediately [Treatment B, Test] and administered direct-to-mouth [Treatment C, Test] versus 1 conventional adult TRIUMEQ tablet [DTG 50 mg/ABC 600 mg/3TC 300 mg] administered direct-to-mouth [Treatment A, Reference] ○ 10 dispersible pediatric TRIUMEQ tablets [DTG 5 mg/ABC 60 mg/3TC 30 mg] administered as a dispersion and taken immediately [Treatment B, Test] versus 10 dispersible pediatric TRIUMEQ tablets [DTG 5 mg/ABC 60 mg/3TC 30 mg] administered direct-to-mouth [Treatment C, Reference]) • In Part 2 of this study, the ln-transformed AUC(0-∞), AUC(0-t), Cmax, and C24 values for DTG and 3TC will be analyzed separately using a mixed effects model, fitting fixed effect terms for period, treatment, and treatment sequence; and treating participant within treatment sequence as a random effect. Point estimates and 90% CIs will be constructed using the residual variance for the following differences of interest: ○ 10 dispersible pediatric DTG/3TC tablets [DTG 5 mg/3TC 30 mg] administered as a dispersion and taken immediately [Treatment E, Test] and administered direct-to-mouth [Treatment F, Test] versus 1 conventional adult DTG tablet [50mg] and 1 conventional 3TC tablet [300 mg] administered direct-to-mouth [Treatment D, Reference] ○ 10 dispersible pediatric DTG/3TC tablets [DTG 5 mg/3TC 30 mg] administered as a dispersion and taken immediately [Treatment E, Test] versus 10 dispersible pediatric DTG/3TC tablets [DTG 5 mg/3TC 30 mg] administered direct-to-mouth [Treatment F, Reference])
Model Checking & Diagnostics
• Refer to Appendix 8: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• Statistical analysis by ANOVA will be presented in tabular format with geometric mean ratios between TRIUMEQ dispersible pediatric tablets versus conventional adult tablets and TIRUMEQ dispersible pediatric tablets administered as a dispersion versus TRIUMEQ dispersible pediatric tablets administered as direct-to-mouth (Part 1) and DTG/3TC dispersible pediatric tablets versus conventional adult tablets and DTG/3TC dispersible pediatric tablets

Pharmacokinetic Statistical Analyses
administered as a dispersion versus DTG/3TC dispersible pediatric tablets administered as direct-to-mouth (Part 2), and 90% CIs for the ratios of AUC(0-∞), AUC(0-t), Cmax, and C24 for DTG, ABC (only for Part 1), and 3TC. Part 1 Example SAS Code: PROC MIXED; CLASS USUBJID TRTA TRTSEQP APERIOD; MODEL LOGPKPARM =TRTA TRTSEQP APERIOD /DDFM=KR; RANDOM USUBJID(TRTSEQP); LSMEANS TRTA; ESTIMATE 'B VS A' TRTA -1 1 0/CL ALPHA=0.1; ESTIMATE 'C VS A' TRTA -1 0 1/CL ALPHA=0.1; ESTIMATE 'B VS C' TRTA 0 1 -1/CL ALPHA=0.1; RUN; Part 2 Example SAS Code: PROC MIXED; CLASS USUBJID TRTA TRTSEQP APERIOD; MODEL LOGPKPARM =TRTA TRTSEQP APERIOD /DDFM=KR; RANDOM USUBJID(TRTSEQP); LSMEANS TRTA; ESTIMATE 'E VS D' TRTA -1 1 0/CL ALPHA=0.1; ESTIMATE 'F VS D' TRTA -1 0 1/CL ALPHA=0.1; ESTIMATE 'E VS F' TRTA 0 1 -1/CL ALPHA=0.1; RUN;

7.1.4. Interim Analysis

7.1.4.1. Overview of Planned Analyses

No interim analysis is planned for this study.

8. SECONDARY STATISTICAL ANALYSES

8.1. Safety Analyses

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

Table 5 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 10: List of Data Displays.

Table 5 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				
Common Non-serious AEs	Y							
Serious AEs	Y			Y				
AEs by Maximum Grade	Y							
Withdrawal AEs				Y				
Laboratory Values								
Clinical Chemistry	Y			Y [2]	Y			
Hematology	Y			Y [2]	Y			
Urinalysis (Dipstick)	Y [5]			Y [2]				
Electrocardiograms (ECGs)								
ECG Findings	Y			Y [3]				
ECG Values	Y			Y [4]				
Vital Signs								
Vital Signs	Y			Y [4]	Y			
Liver								
Liver Events [1]				Y				

NOTES :

1. Conditional display, it will only be produced when an event has occurred.
2. Displays contain only participants with DAIDS toxicities for HIV-infected patients of Grade 2 or higher
3. Displays contain only participants with abnormal findings
4. Displays contain only participants with values of potential clinical importance
5. Displays contain only worst case results relative to baseline

- 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.

8.2. Exploratory Analyses

The exploratory analyses will be based on the "All Participants" population, unless otherwise specified.

Table 6 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 10: List of Data Displays.

Table 6 Overview of Planned Exploratory Analyses

Display Type	Absolute			
	Summary		Individual	
	T	F	F	L
Palatability				
Palatability Questionnaire Results	Y			Y

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- 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 participant observed raw data.

9. REFERENCES

GlaxoSmithKline Document Number 2017N330422_00 (Original – 18-JAN-2018): 2-Part, Phase I, Single-Dose, 3-Period Crossover Relative Bioavailability Study of a Pediatric TRIUMEQ Dispersible Tablet and Pediatric Dolutegravir and Lamivudine (DTG/3TC) Fixed Dose Combination Dispersible Tablet Formulations as Compared With Adult Tablets in Healthy Volunteers (18-JAN-2018)

10. APPENDICES

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

10.1. Appendix 1: Time & Events

10.1.1. Protocol Defined Screening Assessments for Parts 1 and 2

Event	Notes
Informed Consent	
Demographics	
Medical History (includes substance use)	
Inclusion/Exclusion	
Human Immunodeficiency Virus, Hepatitis B and Hepatitis C Screen	
HLA-B*5701	For Part 1 only.
Urine Drug/Alcohol/Cotinine Screen	
Physical Examination	A brief physical examination is required at Screening.
Height, Weight & Body Mass Index	
Vital Sign Measurement	
12-lead Electrocardiogram (Single)	A single repeat evaluation is allowed for eligibility determination.
Follicle-stimulating Hormone and Estradiol (women)	
Pregnancy Test (urine)	For women of child bearing potential (WOCBP) only.
Clinical Laboratory Tests (Chemistry, Hematology, and Urinalysis)	For clinical laboratory tests, see Appendix 2 in the protocol.
Concomitant Medication	

10.1.2. Protocol Defined Time and Events for Parts 1 and 2

Assessments	Periods 1-3							Follow-up	Notes
	Day −1	Day 1			Day 2	Day 3	Day 4		• *Day −1 of Periods 2 and 3 may be the same day as Day 6 of prior periods.* • *At Follow-up, male participants and female participants of non-childbearing potential with no ongoing AEs or vital sign/clinical laboratory results of clinical concern may be followed up virtually by the site via telephone contact.*
		Predose	0 hr	Postdose	24 hr	48 hr	72 hr		
Admission to Unit	X								
Discharge							X		
Outpatient Visit								X	*Follow-up visit will occur 7-10 days after last dose.*
12-lead ECG (single)	X								
Vital signs	X	X		At 4 hours postdose	X			X	• *Single vital sign measurements performed at all time points.* • *Vital signs at Follow-up are only necessary if participant had ongoing AEs or a previous abnormal vital sign result of clinical concern. Only the abnormal value(s) need be re-assessed.*
Brief Physical Examination	X								*Physical examination required only on Day −1 of Period 1 and as needed based on AE assessment.*
Urine Drug/Alcohol/Cotinine	X								• *Drug/Alcohol/Cotinine/pregnancy will be performed as per the standard practice of the site.* • *For clinical laboratory tests, see Appendix 2 in the protocol.* • *Clinical laboratory tests at Follow-up are only necessary if participant had ongoing AEs or a previous abnormal clinical laboratory result of clinical concern. Only the abnormal value(s) need be re-assessed.*
Pregnancy test (serum; WOCBP)	X							X	
Clinical laboratory tests	X				X			X	
Dosing			**X**						*Participants in Part 1 should be provided with an ABC HSR warning card and should be reminded to read it.*
Palatability Assessment				Start within 10 minutes after dose					*Complete for each dispersion treatment (Treatments B & E, see Appendix 4 in the protocol).*
Pharmacokinetic Sampling		X		Collect at: 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 48 and 72 hours postdose before discharge at the end of each period					*Predose is within 15 minutes prior to dosing (see Section 9.5.1 in the protocol).*

Assessments	Periods 1-3							Follow-up	*Notes* • *Day −1 of Periods 2 and 3 may be the same day as Day 6 of prior periods.* • *At Follow-up, male participants and female participants of non-childbearing potential with no ongoing AEs or vital sign/clinical laboratory results of clinical concern may be followed up virtually by the site via telephone contact.*
	Day −1	**Day 1**			**Day 2**	**Day 3**	**Day 4**		
		Predose	**0 hr**	**Postdose**	**24 hr**	**48 hr**	**72 hr**		
Meals	Fasted from 10 hours prior to dosing to 4 hours postdose			Standard for the study centre					
Adverse Events / SAE	X	←==========X==========→						X	
Concomitant medications	X	←==========X==========→						X	

10.2. Appendix 2: Treatment States and Phases

10.2.1. Treatment States

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

10.2.1.1. Treatment States for Safety Data

Treatment State	Definition
Pre-Treatment	Date/Time < Study Treatment Start Date/Time
On-Treatment	Study Treatment Start Date/Time ≤ Date/Time ≤ Study Treatment Stop Date/Time + 6 days
Post-Treatment	Date/Time > Study Treatment Stop Date/Time + 6 days

1. **NOTES:**

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

10.2.1.2. Treatment States for Event Data (e.g. AEs, Concomitant Medications)

Treatment State	Definition
Pre-Treatment	Event Start Date/Time < Initial Study Treatment Date/Time
On-Treatment	If event onset date/time is on or after the initial treatment date/time & on or before the final treatment date/time with 7 days lag time. Initial Study Treatment Date/Time ≤ Event Start Date/Time ≤ Final Study Treatment Date/Time + 6 days
Post-Treatment	If event onset date/time is after the final treatment date/time with 6 days lag time. Event Start Date/Time > Final Study Treatment Date/Time + 6 days
Onset Time Since 1st Dose (Days)	If Treatment Date/Time > Event Onset Date/Time = Event Onset Date – Treatment Date/Time If Treatment Date/Time ≤ Event Onset Date/Time = Event Onset Date/Time – Treatment Date/Time +1 Missing otherwise.
Duration (Days)	Event Resolution Date/Time – Event Onset Date/Time + 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.

10.3. Appendix 3: Data Display Standards & Handling Conventions

10.3.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions				
Study Part	**Treatment Group**		**Data Displays for Reporting**	
	Code	**Description**	**Description[1]**	**Order [2]**
1	A	Adult TRIUMEQ (DTG 50 mg/ABC 600 mg/3TC 300 mg, 1 conventional tablet) administered as direct-to-mouth (reference)	Treatment A	1
	B	Pediatric TRIUMEQ (DTG 5 mg/ABC 60 mg/3TC 30 mg, 10 dispersible tablets) administered as a dispersion and taken immediately (test)	Treatment B	2
	C	Pediatric TRIUMEQ (DTG 5 mg/ABC 60 mg/3TC 30 mg, 10 dispersible tablets) administered as direct-to-mouth (test)	Treatment C	3
2	D	Adult DTG (50 mg, 1 conventional tablet) and adult 3TC (300 mg, 1 conventional tablet) administered as direct-to-mouth (reference)	Treatment D	4
	E	Pediatric DTG/3TC (DTG 5 mg/3TC 30 mg, 10 dispersible tablets) administered as a dispersion and taken immediately (test)	Treatment E	5
	F	Pediatric DTG/3TC (DTG 5 mg/3TC 30 mg, 10 dispersible tablets) administered as direct-to-mouth (test)	Treatment F	6

NOTES:

1. The word “Treatment” may be omitted from displays in order to limit wrapping
2. Order represents treatments being presented in TFL, as appropriate.

- Where applicable, outputs will include a treatment footnote describing the treatments: “Treatment A = Adult TRIUMEQ (DTG 50 mg/ABC 600 mg/3TC 300 mg, 1 conventional tablet) administered as direct-to-mouth (reference); Treatment B = Pediatric TRIUMEQ (DTG 5 mg/ABC 60 mg/3TC 30 mg, 10 dispersible tablets) administered as a dispersion and taken immediately (test); Treatment C = Pediatric TRIUMEQ (DTG 5 mg/ABC 60 mg/3TC 30 mg, 10 dispersible tablets) administered as direct-to-mouth (test); Treatment D = Adult DTG (50 mg, 1 conventional tablet) and adult 3TC (300 mg, 1 conventional tablet) administered as direct-to-mouth (reference); Treatment E = Pediatric DTG/3TC (DTG 5 mg/3TC 30 mg, 10 dispersible tablets) administered as a dispersion and taken immediately (test); Treatment F = Pediatric DTG/3TC (DTG 5 mg/3TC 30 mg, 10 dispersible tablets) administered as direct-to-mouth (test).”

10.3.2. Baseline Definition & Derivations

10.3.2.1. 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 first dose, unless noted otherwise. Baseline definitions are applicable to each period. For later periods, Day -1 may be the same day as Day 6 of the prior period.

Parameter	Study Assessments Considered As Baseline			Baseline Used in Data Display
	Screening	Day -1	Day 1 (Pre-Dose)	
Safety				
Hematology	X	X		Day -1
Clinical Chemistry	X	X		Day -1
12-Lead ECG	X	X		Day -1
Vital Signs	X	X	X	Day 1 (Pre-Dose)

NOTES :

- Unless otherwise stated, the mean of replicate assessments at any given time point will be used as the value for that time point.

10.3.2.2. 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 10.3.2.1 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.

10.3.3. Reporting Process & Standards

Reporting Process
Software
• The currently supported versions of SAS 9.3 or higher and Phoenix WinNonlin software 6.4 or higher will be used.
Analysis Datasets
• Analysis datasets will be created according to CDISC standards SDTM IG Version 3.2 & ADaM IG Version 1.0. • For creation of ADaM datasets (ADCM/ADAE), the same version of dictionary datasets will be implemented for conversion from SI to SDTM.
Generation of RTF Files
• RTF files will be generated for all reporting efforts described in the RAP.

Reporting Standards	
General	
• The current GSK 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 participant received unless otherwise stated. • GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places 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. • 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 (with the exception of individual PK concentration-time figures, where actual relative time will be used), 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 participant's listings. • 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 • NQs at the beginning of a participant profile (i.e. before the first incidence of a measurable concentration) are deemed to be zero as it is assumed that in this circumstance no drug is yet measurable in the blood. • For NQs at the end of the participant profile (i.e. after the last incidence of a measurable concentration); • for individual plots and pharmacokinetic analyses these are dropped (set to missing) as they do not provide any useful information (and can erroneously indicate that absolutely no drug is present)

Reporting Standards	
	• for summary statistics these are set to 0 (to avoid skewing of the summary statistics) • Individual NQs which fall between two measurable concentrations are set to missing (individual values of this nature are assumed to be an anomaly) • If two or more NQ values occur in succession between measurable concentrations, the profile will be deemed to have terminated at the last measurable concentration prior to these NQs. For the purpose of individual participant plots, these NQs will be set to 0, and the subsequent measurable concentrations will be retained. For the derivation of pharmacokinetic parameters, these NQs and any subsequent measurable concentrations will be omitted (set to missing).
Categorical Data	N (number of participants in subgroup), n (number of participants with evaluable data), 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 (Ln-Transformed)	N (number of participants in subgroup), n (number of participants with evaluable data), geometric mean, 95% CI of geometric mean, standard deviation (SD) of logged data and between geometric coefficient of variation (CVb (%)) will be reported. CV_b (%) = square root of (exp(SD^2) – 1) * 100 (SD = SD of ln-transformed data)
Parameters Not Being Ln-Transformed	Tmax, Tlast, tlag, first point, last point, and number of points used in the determination of λz, %AUCex.
Summary Tables	The following PK parameters will not be summarised: first point, last point, and number of points used in the determination of λz and Rsq_adjusted.
Listings	Include the first point, last point and number of points used in the determination of λz. nd Rsq_adjusted for listings
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

10.4. Appendix 4: Derived and Transformed Data

10.4.1. 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. • Participants having both High and Low values for Normal Ranges at any post-baseline visits 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 randomisation date:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < Randomisation Date → Study Day = Ref Date – Randomisation Date
  • Ref Data ≥ Randomisation Date → Study Day = Ref Date – (Randomisation Date) + 1

10.4.2. Study Population

Demographics
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]**

10.4.3. 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: $$RR = \left[\left(\frac{QT}{QTcB}\right)^2\right] * 1000$$ [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: $QTcB = \frac{QT}{\sqrt{\frac{RR}{1000}}}$ $QTcF = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$

Adverse Events
AEs of Special Interest
• No analysis for AEs of Special Interest will be performed

10.5. Appendix 5: Premature Withdrawals & Handling of Missing Data

10.5.1. Premature Withdrawals

Element	Reporting Detail
General	• Participant study completion (i.e. as specified in the protocol) was defined as completing all phases of the study including the follow-up visit. • Withdrawn participants may be 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.

10.5.2. 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 participant 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.

10.5.2.1. Handling of Missing Dates

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

AEs	• 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 2: Treatment States and Phases.
	  ○ 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.

Element	Reporting Detail
	• Start or end dates which are completely missing (i.e. no year specified) will remain missing, with no imputation applied.

10.5.2.2. 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: 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 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.

10.6. Appendix 6: Values of Potential Clinical Importance

10.6.1. ECG

ECG Parameter	Units	Potential Clinically Important Range	
		Lower	Upper
Absolute			
Absolute QTc Interval	msec	> 450[1]	
		> 450[2]	≤ 479[2]
		≥ 480[2]	≤ 499[2]
		≥ 500[2]	
Absolute PR Interval	msec	< 110[1]	> 220[1]
Absolute QRS Interval	msec	< 75[1]	> 110[1]
Change from Baseline			
Increase from Baseline QTc	msec	≤ 30[2]	
	msec	> 30[1]	≤ 59[2]
	msec	≥ 60[2]	

NOTES:

1. Represent standard ECG values of PCI for HV studies.
2. Represent further subdivisions of ECG values for analysis.

10.6.2. Vital Signs

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

10.7. Appendix 7: Multiple Comparisons & Multiplicity

10.7.1. Handling of Multiple Comparisons & Multiplicity

No adjustments for multiplicity will be made.

10.8. Appendix 8: Model Checking and Diagnostics for Statistical Analyses

10.8.1. Statistical Analysis Assumptions

Endpoint(s)	• PK endpoints AUC(0-∞), AUC(0-t), Cmax, and C24
Analysis	• Mixed Effects

Assumptions:

- Model assumptions will be applied, but appropriate adjustments may be made 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.

10.9. Appendix 9 – Abbreviations & Trade Marks

10.9.1. Abbreviations

Abbreviation	Description
3TC	Lamivudine
ABC	Abacavir
ADaM	Analysis Data Model
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-∞)	Area under the concentration-time curve from time 0 (predose) extrapolated to infinite time
%AUCex	The percentage of AUC(0-∞) obtained by extrapolation
BA	Bioavailability
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
CPK	Creatine phosphokinase
Ct	The last observed quantifiable concentration
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
HSR	Hypersensitivity reaction
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
SAC	Statistical Analysis Complete

Abbreviation	Description
SAS	Statistical Analysis Software
SD	Standard deviation
SDTM	Study Data Tabulation Model
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

10.9.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
TRIUMEQ

Trademarks not owned by the GlaxoSmithKline Group of Companies
Phoenix WinNonlin
SAS

10.10. Appendix 10: List of Data Displays

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.7	NA
Safety	2.1 to 2.16	NA
Pharmacokinetic	3.1 to 3.14	3.1 to 3.21
Exploratory (Palatability)	4.1	NA
Section	**Listings**	
ICH Listings	1 to 37	
Other (non-ICH) Listings	38 to 45	

10.10.1. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln
Exploratory (Palatability)	EXP_Fn	EXP_Tn	EXP_Ln

NOTES:

- Non-Standard displays are indicated in the 'IDSL / TST ID / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

10.10.2. Deliverable [Priority]

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

NOTES:

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

10.10.3. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Participant Disposition and Populations					
1.1	Enrolled	NS1	Summary of Number of Participants Enrolled by Country and Site ID		SAC [1]
1.2	All Participants	ES1A	Summary of Participant Disposition for the Participant Conclusion Record		SAC [1]
1.3	Screened	ES6	Summary of Screening Status and Reasons for Screen Failures		SAC [1]
1.4	Screened	DV1	Summary of Important Protocol Deviations		SAC [1]
Demographics					
1.5	All Participants	DM3	Summary of Demographic Characteristics		SAC [1]
1.6	All Participants	DM5	Summary of Race and Racial Combinations		SAC [1]
1.7	All Participants	DM11	Summary of Age Ranges		SAC[1]

10.10.4. Safety Tables

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
2.1	All Participants	AE1CP	Summary of All Adverse Events by System Organ Class and Preferred Term		SAC [1]
2.2	All Participants	AE1CP	Summary of Drug-Related Adverse Events		SAC [1]
2.3	All Participants	AE15	Summary of Common (>=5%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)		SAC [1]
2.4	All Participants	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)		SAC[1]
2.5	All Participants	AE5A	Summary of Adverse Events by Maximum Grade by System Organ Class and Preferred Term		SAC [1]
Laboratory Values					
2.6	All Participants	LB1	Summary of Clinical Chemistry Values		SAC [1]
2.7	All Participants	LB1	Summary of Clinical Chemistry Values Change from Baseline		SAC [1]
2.8	All Participants	BL	Summary of Clinical Chemistry Results by Maximum Grade Increase Post-Baseline Relative to Baseline		SAC [1]
2.9	All Participants	LB1	Summary of Hematology Values		SAC [1]
2.10	All Participants	LB1	Summary of Hamatology Values Change from Baseline		SAC [1]
2.11	All Participants	LB16	Summary of Hematology Results by Maximum Grade Increase Post-Baseline Relative to Baseline		SAC [1]

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.12	All Participants	UR1	Summary of Worst Case Urinalysis Results Post-Baseline Relative to Baseline		SAC [1]
Electrocardiograms					
2.13	All Participants	EG1	Summary of ECG Findings		SAC [1]
2.14	All Participants	EG2	Summary of ECG Values		SAC [1]
Vital Signs					
2.15	All Participants	VS1	Summary of Values in Vital Signs		SAC[1]
2.16	All Participants	VS1	Summary of Change from Baseline in Vital Signs		SAC[1]

10.10.5. Pharmacokinetic Tables

Pharmacokinetic : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentration Data					
3.1	PK	PKCT1	Summary of DTG Plasma Pharmacokinetic Concentration-Time Data by Study Part and Treatment		SAC [1]
3.2	PK	PKCT1	Summary of ABC Plasma Pharmacokinetic Concentration-Time Data by Treatment	Part 1 only	SAC [1]
3.3	PK	PKCT1	Summary of 3TC Plasma Pharmacokinetic Concentration-Time Data by Study Part and Treatment		SAC [1]
PK Derived Parameters					
3.4	PK	PKPT4	Summary of Derived DTG Plasma Pharmacokinetic Parameters (Non-Transformed) by Study Part and Treatment	Parameters with units	SAC [1]
3.5	PK	PKPT4	Summary of Derived DTG Plasma Pharmacokinetic Parameters (Ln-Transformed) by Study Part and Treatment	Parameters with units	SAC [1]
3.6	PK	PKPT4	Summary of Derived ABC Plasma Pharmacokinetic Parameters (Non-Transformed) by Treatment	Parameters with units; Part 1 only	SAC [1]
3.7	PK	PKPT4	Summary of Derived ABC Plasma Pharmacokinetic Parameters (Ln-Transformed) by Treatment	Parameters with units; Part 1 only	SAC [1]
3.8	PK	PKPT4	Summary of Derived 3TC Plasma Pharmacokinetic Parameters (Non-Transformed) by Study Part and Treatment	Parameters with units	SAC [1]
3.9	PK	PKPT4	Summary of Derived 3TC Plasma Pharmacokinetic Parameters (Ln-Transformed) by Study Part and Treatment	Parameters with units	SAC [1]

Pharmacokinetic : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Analysis Tables					
3.10	PK	PKPT3	Statistical Analysis of DTG Plasma Pharmacokinetic Parameters, Study Part 1	AUC(0-t), AUC(0-∞), Cmax and C24 only by Treatment. Part 1 only.	SAC [1]
3.11	PK	PKPT3	Statistical Analysis of DTG Plasma Pharmacokinetic Parameters, Study Part 2	AUC(0-t), AUC(0-∞), Cmax and C24 only by Treatment. Part 2 only.	SAC [1]
3.12	PK	PKPT3	Statistical Analysis of ABC Plasma Pharmacokinetic Parameters, Study Part 1	AUC(0-t), AUC(0-∞), Cmax and C24 only by Treatment. Part 1 only.	SAC [1]
3.13	PK	PKPT3	Statistical Analysis of 3TC Plasma Pharmacokinetic Parameters, Study Part 1	AUC(0-t), AUC(0-∞), Cmax and C24only by Treatment. Part 1 only.	SAC [1]
3.14	PK	PKPT3	Statistical Analysis of 3TC Plasma Pharmacokinetic Parameters, Study Part 2	AUC(0-t), AUC(0-∞), Cmax and C24only by Treatment. Part 2 only.	SAC [1]

10.10.6. Pharmacokinetic Figures

Pharmacokinetic : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Individual Concentration Plots					
3.1	PK	PKCF1X	Individual DTG Plasma Concentration-Time Plots by Participant (Linear and Semi-Logarithmic)	Paginate by Participant	SAC [1]
3.2	PK	PKCF1X	Individual ABC Plasma Concentration-Time Plots by Participant (Linear and Semi-Logarithmic)	Paginate by Participant; Part 1 only	SAC [1]
3.3	PK	PKCF1X	Individual 3TC Plasma Concentration-Time Plots by Participant (Linear and Semi-Logarithmic)	Paginate by Participant	SAC [1]
Mean / Median Concentration Plots					
3.4	PK	PKCF2	Mean DTG Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	All treatments for each Part on one page	SAC [1]
3.5	PK	PKCF2	Median DTG Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	All treatments for each Part on one page	SAC [1]
3.6	PK	PKCF2	Mean ABC Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	All treatments for Part 1 on one page	SAC [1]
3.7	PK	PKCF3	Median ABC Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	All treatments for Part 1 on one page	SAC [1]
3.8	PK	PKCF3	Mean 3TC Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	All treatments for each Part on one page	SAC [1]
3.9	PK	PKCF3	Median 3TC Plasma Concentration-Time Plots by Treatment (Linear and Semi-Logarithmic)	All treatments for each Part on one page	SAC [1]

Pharmacokinetic : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Analysis Plots					
3.10	PK	PKPF3	Comparative Plot of Individual DTG Plasma Cmax by Treatment (Linear and Semi-Logarithmic)	All treatments for each Part on one page	SAC [1]
3.11	PK	PKPF3	Comparative Plot of Individual DTG Plasma AUC(0-t) by Treatment (Linear and Semi-Logarithmic)	All treatments for each Part on one page	SAC [1]
3.12	PK	PKPF3	Comparative Plot of Individual DTG Plasma AUC(0-∞) by Treatment (Linear and Semi-Logarithmic)	All treatments for each Part on one page	SAC [1]
3.13	PK	PKPF3	Comparative Plot of Individual DTG Plasma C24 by Treatment (Linear and Semi-Logarithmic)	All treatments for each Part on one page	SAC [1]
3.14	PK	PKPF3	Comparative Plot of Individual ABC Plasma Cmax by Treatment (Linear and Semi-Logarithmic)	All treatments for Part 1 on one page	SAC [1]
3.15	PK	PKPF3	Comparative Plot of Individual ABC Plasma AUC(0-t) by Treatment (Linear and Semi-Logarithmic)	All treatments for Part 1 on one page	SAC [1]
3.16	PK	PKPF3	Comparative Plot of Individual ABC Plasma AUC(0-∞) by Treatment (Linear and Semi-Logarithmic)	All treatments for Part 1 on one page	SAC [1]
3.17	PK	PKPF3	Comparative Plot of Individual ABC Plasma C24 by Treatment (Linear and Semi-Logarithmic)	All treatments for Part 1 on one page	SAC [1]
3.18	PK	PKPF3	Comparative Plot of Individual 3TC Plasma Cmax by Treatment (Linear and Semi-Logarithmic)	All treatments for each Part on one page	SAC [1]
3.19	PK	PKPF3	Comparative Plot of Individual 3TC Plasma AUC(0-t) by Treatment (Linear and Semi-Logarithmic)	All treatments for each Part on one page	SAC [1]
3.20	PK	PKPF3	Comparative Plot of Individual 3TC Plasma AUC(0-∞) by Treatment (Linear and Semi-Logarithmic)	All treatments for each Part on one page	SAC [1]
3.21	PK	PKPF3	Comparative Plot of Individual 3TC Plasma C24 by Treatment (Linear and Semi-Logarithmic)	All treatments for each Part on one page	SAC [1]

10.10.7. Exploratory Tables

Exploratory : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Palatability					
4.1	All Participants	EXP_T1	Summary of Palatability Questionnaire Results (Part 1, Treatment B and Part 2, Treatment E Only)		SAC[1]

10.10.8. ICH Listings

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Randomisation					
1	All Participants	CP_TA2	Listing of Randomized and Actual Treatment		SAC [1]
Participant Disposition					
2	All Participants	ES3	Listing of Reasons for Study Withdrawal		SAC [1]
3	Screened	ES7	Listing of Reasons for Screen Failure		SAC [1]
4	Screened	DV2A	Listing of Important Protocol Deviations		SAC [1]
5	All Participants	IE4	Listing of Participants with Inclusion/Exclusion Criteria Deviations		SAC[1]
6	Enrolled	SP3	Listing of Participants Excluded from Any Population		SAC [1]
7	Enrolled	SAFE_L4	Listing of Participants in Previous Clinical Trial		SAC [1]

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Demographics					
8	All Participants	DM4	Listing of Demographic Characteristics		SAC [1]
9	All Participants	DM10	Listing of Race		SAC [1]
Concomitant Medications					
10	All Participants	CM4	Listing of Concomitant Medications		SAC[1]
Exposure					
11	All Participants	SAFE_L1	Listing of Exposure Data		SAC[1]
Adverse Events					
12	All Participants	AE2	Listing of Relationship Between System Organ Class and Verbatim Text		SAC[1]
13	All Participants	AE7	Listing of Subject Numbers for Individual Adverse Events		SAC[1]
14	All Participants	AE9CP	Listing of All Adverse Events		SAC[1]
15	All Participants	AE9CP	Listing of Study Drug Related Adverse Events		SAC[1]
16	All Participants	SAFE_L2	Listing of Serious Adverse Events		SAC[1]
17	All Participants	AE9CP	Listing of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study		SAC[1]
18	All Participants	SAFE_L3	Listing of Liver Adverse Events		SAC[1]

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
19	All Participants	AE14	Listing of Reasons for Considering as a Serious Adverse Event		SAC[1]
Laboratory Values					
20	All Participants	LB6	Listing of Clinical Chemistry Toxicities of Grade 2 or Higher		SAC [1]
21	All Participants	LB6	Listing of All Clinical Chemistry Data for Participants with Toxicities of Grade 2 or Higher		SAC [1]
22	All Participants	LB6	Listing of Hematology Toxicities of Grade 2 or Higher		SAC [1]
23	All Participants	LB6	Listing of All Hematology Data for Participants with Toxicities of Grade 2 or Higher		SAC [1]
24	All Participants	LB6	Listing of Urinalysis Toxicities of Grade 2 or Higher		SAC [1]
25	All Participants	LB6	Listing of All Urinalysis Data for Participants with Toxicities of Grade 2 or Higher		SAC [1]
Electrocardiograms					
26	All Participants	EG6	Listing of Abnormal ECG Findings		SAC [1]
27	All Participants	EG6	Listing of All ECG Findings for Participants with an Abnormal Finding		SAC [1]
28	All Participants	EG4	Listing of ECG Values of Potential Clinical Importance		SAC [1]
29	All Participants	EG4	Listing of All ECG Values for Participants with any Value of Potential Clinical Importance		SAC[1]

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Vital Signs					
30	All Participants	VS5	Listing of Vital Signs of Potential Clinical Importance		SAC [1]
31	All Participants	VS5	Listing of All Vital Signs for Participants with any Value of Potential Clinical Importance		SAC [1]
Liver Event					
32	All Participants	LIVER5	Listing of Liver Monitoring/Stopping Event Reporting		SAC[1]
33	All Participants	MH3	Listing of Medical Conditions for Participants with Liver Stopping Events		SAC[1]
34	All Participants	SAFE_L5	Listing of Alcohol Intake at Onset of Liver Event		SAC[1]
35	All Participants	PKCL1X	Listing of Plasma Concentration Data for Participants with Liver Stopping Events		SAC[1]
36	All Participants	LIVER7	Listing of Liver Biopsy Details		SAC[1]
37	All Participants	LIVER8	Listing of Liver Imaging Details		SAC[1]

10.10.9. Other (non-ICH) Listings

Other (non-ICH) : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pharmacokinetic					
38	PK	PKCL1X	Listing of DTG Plasma Pharmacokinetic Concentration-Time Data by Treatment	Please list all the concentration data including unscheduled. Repeat for all treatments and Parts.	SAC [1]
39	PK	PKCL1X	Listing of ABC Plasma Pharmacokinetic Concentration-Time Data by Treatment	Please list all the concentration data including unscheduled. Repeat for all treatments of Part 1.	SAC [1]
40	PK	PKCL1X	Listing of 3TC Plasma Pharmacokinetic Concentration-Time Data by Treatment	Please list all the concentration data including unscheduled. Repeat for all treatments and Parts.	SAC [1]
41	PK	PKPL1X	Listing of Derived DTG Plasma Pharmacokinetic Parameters by Treatment	Repeat for all treatments and Parts.	SAC [1]
42	PK	PKPL1X	Listing of Derived ABC Plasma Pharmacokinetic Parameters by Treatment	Repeat for all treatments of Part 1.	SAC [1]
43	PK	PKPL1X	Listing of Derived 3TC Plasma Pharmacokinetic Parameters by Treatment	Repeat for all treatments and Parts.	SAC [1]
Exploratory					
44	All Participants	EXP_L1	Listing of Palatability Questionnaire Results (Part 1, Treatment B Only)		SAC[1]
45	All Participants	EXP_L1	Listing of Palatability Questionnaire Results (Part 2, Treatment E Only)		SAC[1]

10.11. Appendix 11: Example Mock Shells for Data Displays

Available upon request