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

Title	:	Reporting and Analysis Plan for a non-randomized, sequential, fixed-sequence evaluation of prototype dolutegravir liquid formulations versus 5mg dolutegravir dispersible tablets following single-dose fasted-state administrations to normal healthy adult participants
Compound Number	:	GSK1349572
Effective Date	:	17-Apr-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 209354.
- This RAP is intended to describe the final 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.

RAP Author(s):

Author	Date
PPD Senior Statistician (Infectious Diseases, Clinical Statistics)	17-Apr-2019.

RAP Team Review Confirmations (Method: E-mail):

Reviewer	Date
PPD Programming Manager (Infectious Diseases, Clinical Programming)	14-Apr-2019
PPD Global Clinical Development Director (Infectious Diseases, R&D PCPS GCSD)	12-Apr-2019
PPD, FCP MSc Director (Clinical Development, Research and Development, ViiV Healthcare)	12-Apr-2019
PPD Director (Clinical Pharmacology, ViiV Healthcare)	12-Apr-2019
PPD Director (Clinical Pharmacology Modelling and Simulation)	15-Apr-2019
PPD Principal Statistician (Dolutegravir Statistics)	15-Apr-2019

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

Approver	Date
PPD Statistics Director (Infectious Diseases, Clinical Statistics) [pharma TMF e-Signature]	17-Apr-2019
PPD Programming Director (Infectious Diseases, Clinical Programming) [email approval]	16-Apr-2019

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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:

Revision Chronology:		
2018N379348_00	29-Oct-2018	Original
2018N379348_01	27-Feb-2019	The original protocol was written assuming that a greater number of prototype formulations would possibly have been tested in the study. Pre-clinical testing yielded only 2 prototypes suitable to take forward clinically. This amendment clarifies the study design for only 2 test formulations.

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 amendment 01 [(Dated: 27/Feb/2019)].

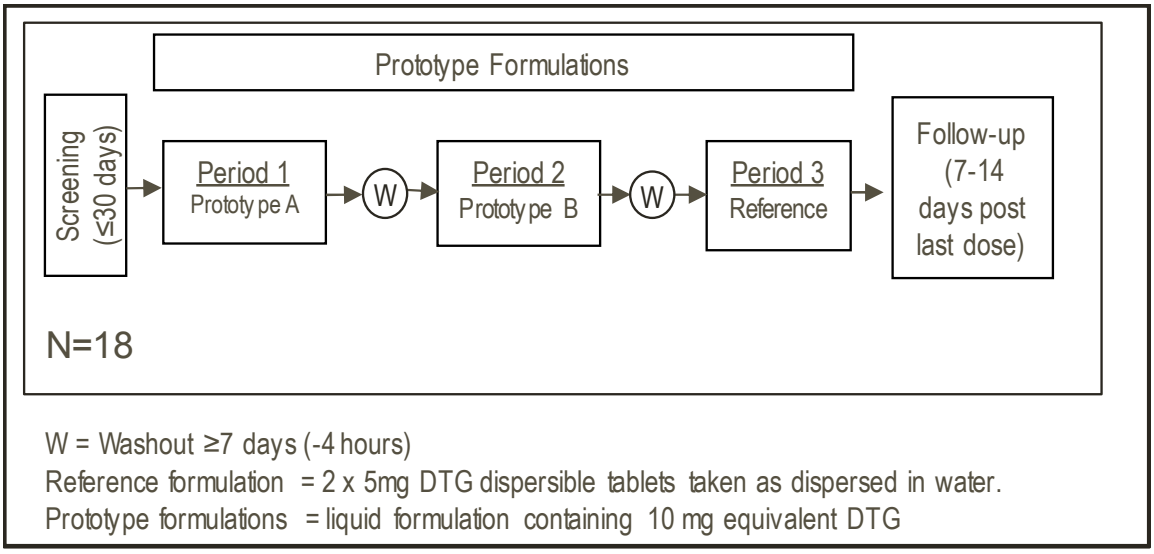
2.2. Study Objective(s) and Endpoint(s)

Objectives	**Endpoints**
Primary Objectives	**Primary Endpoints**
To evaluate the relative bioavailability of equivalent doses of single dose prototype liquid formulations containing 10mg equivalent DTG compared to a single dose of 2 x 5mg dispersible DTG tablet dispersed in water.	Plasma DTG • $AUC_{(0-t)}$ • $AUC_{(0-\infty)}$ • C_{max}
Secondary Objectives	**Secondary Endpoints**
To characterize the pharmacokinetics of equivalent doses of a single dose of prototype liquid formulations containing 10mg equivalent DTG and a single dose of 2 x 5mg dispersible DTG tablet dispersed in water.	Plasma DTG • t_{lag} • t_{max} • t_{last} • $t_{½}$ • λz • $\%AUC_{ex}$ • $AUC_{(0-24)}$ • $AUC_{(0-72)}$ • CL/F and Vz/F • Ct • C_{24} of each formulation
To assess the safety and tolerability from single-dose administration of prototype liquid formulations containing 10mg equivalent DTG in healthy participants in a fasted state.	Safety and tolerability parameters as assessed by change from baseline in vital signs (BP and HR), number of participants with adverse events and toxicity grading of clinical laboratory tests.

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

2.3. Study Design

Overview of Study Design and Key Features



Design Features	• This is an open-label, single-centre, single dose study in healthy adult participants to assess prototype liquid formulations with 2 x 5mg DTG Dispersible tablet as reference. • The study is a non-randomized 3-period, sequential, 3-way fixed-sequence design in which 2 prototype liquid formulations will be evaluated following single-dose administrations in the fasted state.
Dosing	Periods 1, 2 and 3 will evaluate a single reference dose (2 x 5mg dispersible DTG tablet dispersed in water) and 2 liquid prototype DTG formulations (containing a target total dose of 10mg DTG).
Time & Events	Refer to Appendix 2: Schedule of Activities
Treatment Assignment	This is an open-label, non-randomized study wherein all the subjects will be part of Period 1, 2 and 3.
Interim Analysis	There will be no formal interim analyses. However, an analyses of nominal time PK data will be performed after the final dosing session of the study. Treatment and period information will be used in the analyses.

2.4. Statistical Hypotheses

This study is designed to estimate the relative bioavailability of two experimental liquid formulations of DTG relative to DTG dispersible tablets dispersed in water and dosed in the fasted state.

No formal hypotheses will be tested.

For each pharmacokinetic endpoint (except t_{max} and t_{lag}), point estimates of the geometric mean of each prototype treatment and Reference Treatment are estimated. The ratio of the two estimates (GMR), μ (prototype)/μ (reference), and its corresponding 90% confidence interval will be constructed.

3. PLANNED ANALYSES

3.1. Interim Analyses

There will be no formal interim analyses.

3.2. 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.
3. The study has a non-randomised open label design; however, for internal study reporting, subjects will be assigned randomisation numbers. Therefore, the formal process for unblinding the randomization codes is required.
4. Randomization codes have been distributed according to RandAll NG procedures.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	• All participants who sign the ICF	Screen Failures
Enrolled	• All participants who passed screening and entered the study. • Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Reserve, Not Used) are excluded from the Enrolled population as they did not enter the study.	Study Population (Selected Outputs)
All Participants/Safety	• All participants who were randomized and received at least one dose of study medication. • This population will be used for the study population and safety displays.	• Study Population • Safety
Pharmacokinetic (PK)	• Participants in the 'All Participants' population for whom a pharmacokinetic sample was obtained and had evaluable PK assay results. • PK population will be the population for reporting of PK data.	PK

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

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 are captured and categorised in 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			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order in TLF
A	Prototype A	Prototype A	1
B	Prototype B	Prototype B	2
R	2x5mg DTG Dispersible Tablets dispersed in water	DTG Ref	3

Treatment comparisons will be displayed as follows using the descriptors as specified:

1. Prototype A vs DTG Reference Treatment
2. Prototype B vs DTG Reference Treatment

5.2. Baseline Definitions

For all endpoints (except as noted in baseline definitions) the baseline value will be the last pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

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

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

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
10.3	Appendix 3: Study Phases and Treatment Emergent Adverse Events
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

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the "All Participants" population, unless otherwise specified. Screen failures will be summarised or listed based on the "Screened" population.

Study population analyses including analyses of subject's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, and exposure and treatment compliance will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 9: List of Data Displays.

6.2. Details of Planned Study Population Summaries

Participant Disposition

Participant Disposition for the Subject Conclusion Record

The number and percentage of participants who completed the study as well as participants who withdrew from the study will be summarized. Reason for withdrawal will also be summarized for participants who withdrew from the study. Only the total column will appear.

Treatment Status and Reasons for Discontinuation of Study Treatment

A summary of the number and percentage of subjects who completed the study treatment as planned as well as subjects who stopped study treatment prematurely will be produced. Only the total column will appear.

Screening Status and Reasons for Screen Failure

This will be based on Screened population. The number and percentage of subjects who passed screening and who failed screening will be summarized along with the reasons for screen failure. Only the total column will appear.

Number of Subjects Enrolled by Country and Site ID

This will be based on Enrolled population. The number of subjects summarized by Country, Site ID and Investigator name will be presented. Only the total column will appear.

Protocol Deviations

Important Protocol Deviations

The number and percentage of subjects who had important protocol deviations defined as part of the protocol deviation management plan for the study, will be summarized. Only the total column will appear.

Demographic and Baseline Characteristics

Demographic Characteristics

The number and percentage of subjects or summary statistics will be provided for each demographic characteristic and only the total column will appear: Sex, Age (years), Age Group (years), Ethnicity, Race detail, Height, Weight, and Body Mass Index. Age Group (years) will be categorized into three ('≤18', '19-55', '≥56'). Each demographic characteristic will be summarized using the minimum set of summary statistics.

Age Ranges

This will be based on Enrolled population. The number and percentage of subjects within each age range category will be provided. Only the total column will appear. Only age ranges that are applicable to the study will be included (i.e., only '18-55 years'). This is based on the standard of EMA clinical trial results disclosure requirements.

Race and Racial Combinations

The five high level FDA race categories and designated Asian subcategories will be summarised along with all combinations of high level categories which exist in the data. Only the total column will appear.

Prior and Concomitant Medications

All prior and concomitant medications will be summarized based on the definition specified in Appendix 3 later in the document.

7. SAFETY ANALYSES

The safety analyses will be based on the "All Participants" population, unless otherwise specified. No formal statistical analysis of the safety data will be conducted.

Unless stated otherwise, descriptive summaries for continuous variables will include n, mean, standard deviation (SD), median, minimum, maximum; whereas, n and percent will be used as summary statistics for categorical variable.

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. Tables will present AEs in the treatment phase. Listings will present all AEs. The details of the planned displays are provided in Appendix 9: List of Data Displays.

7.1.1. Details of Planned Adverse Event Summaries

Summaries will be provided by Period (Prototype A, Prototype B, DTG Reference Treatment) unless otherwise specified.

Adverse Events (AEs)

All AEs by SOC and PT

The number and percentage of subjects with all relevant adverse events will be summarized by MedDRA System Organ Class and Preferred Term by treatment group and total. The counting of events and the percentages will be based on the number of subjects on each treatment, so subjects may appear in more than one treatment category.

All AEs by Maximum Grade by SOC and PT

The number and percentage of subjects with adverse events by grade will be summarized by MedDRA System Organ Class and Preferred Term by treatment group and total. The counting of events and the percentages will be based on the number of subjects on each treatment, so subjects may appear in more than one treatment category.

Drug-related AEs by SOC and PT

The number and percentage of subjects with all drug-related adverse events will be summarized by MedDRA System Organ Class and Preferred Term by treatment group and total. The counting of events and the percentages will be based on the number of subjects on each treatment, so subjects may appear in more than one treatment category.

Drug-related AEs by Maximum Grade by SOC and PT

The number and percentage of subjects with drug-related adverse events by grade will be summarized by MedDRA System Organ Class and Preferred Term by treatment group

and total. The counting of events and the percentages will be based on the number of subjects on each treatment, so subjects may appear in more than one treatment category.

Common AEs

Summaries of the number and percentage of subjects with common (incidence greater than five percent) adverse events by overall frequency will be displayed for grade 2-4 events, non-serious events by SOC and PT, and drug related grade 2-4 events. The counting of events and the percentages will be based on the number of subjects on each treatment, so subjects may appear in more than one treatment category.

Serious Adverse Events

Serious AEs by SOC and PT

The number and percentage of subjects with serious adverse events will be summarized by MedDRA System Organ Class and Preferred Term by treatment group and total. The counting of events and the percentages will be based on the number of subjects on each treatment, so subjects may appear in more than one treatment category.

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. All laboratory data will be summarized and listed. The details of the planned displays are in Appendix 9: List of Data Displays.

7.2.1. Details of Planned Laboratory Summaries

Changes from Baseline

Changes in value from baseline for each quantitative laboratory test will be summarised at every assessed time point using descriptive statistics defined above.

Worst Case Laboratory Results by PCI Criteria Post-Baseline Relative to Baseline

The number of subjects with worst case laboratory results relative potential clinical importance (PCI) criteria which are post-baseline relative to baseline will be summarized by laboratory test and category.

Laboratory Results by Maximum Grade Increases Post-Baseline Relative to Baseline

The number of subjects with laboratory results will be summarized by laboratory test, term (e.g. CTCAE term), maximum grade increase (e.g., Increase to Grade 1, Increase to Grade 2, Increase to Grade 3, Increase to Grade 4) and maximum grade increase subtotals (e.g., Increase to Grades 1 to 4, Increase to Grades 2 to 4, Increase to Grades 3 to 4). Hepatobiliary results will also be summarized.

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. Change from baseline in vital signs will be summarized descriptively. All ECG and vital signs data will be listed. The details of the planned displays are presented in Appendix 9: List of Data Displays.

8. PHARMACOKINETIC ANALYSES

8.1. Primary Pharmacokinetic Analyses

8.1.1. Endpoint / Variables

8.1.1.1. Drug Concentration Measures

Refer to Appendix 4: Data Display Standards & Handling Conventions (Section 10.4.3 Reporting Standards for Pharmacokinetic)

8.1.1.2. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters of DTG 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
$AUC_{(0-t)}$ (h*ng/mL)	The area under the concentration-time curve from zero time (pre-dose) to the time of last quantifiable concentration (AUC(0-t)) will be calculated by a combination of linear and logarithmic trapezoidal methods. The linear trapezoidal method will be employed for all incremental trapezoids arising from increasing concentrations and the logarithmic trapezoidal method will be used for those arising from decreasing concentrations (i.e., Linear Up/Log Down calculation method in Phoenix WinNonlin Professional).
$AUC_{(0-inf)}$ (h*ng/mL)	The area under the concentration-time curve from zero time (pre-dose) extrapolated to infinite time ($AUC_{(0-inf)}$) will be calculated as follows: $AUC_{(0-inf)} = AUC_{(0-t)} + C_t / \lambda_z$
C_{max} (ng/mL)	Maximum observed plasma concentration following each dose will be obtained directly from the concentration-time data.

NOTES:

- Additional parameters may be included as required.
- C_t is the last observed quantifiable concentration.
- λ_z is the first order rate constant associated with the terminal (log-linear) portion of the curve.

8.1.2. Summary Measure

The ratio of geometric means for $AUC_{(0-t)}$, $AUC_{(0-inf)}$ and C_{max} of DTG between each of the prototypes and DTG reference treatment will be used for the comparison between Prototype A vs. DTG Reference Treatment, and Prototype B vs. DTG Reference Treatment.

8.1.3. Population of Interest

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

8.1.4. Strategy for Intercurrent (Post-Randomization) Events

Intercurrent events which may affect the evaluation of bioequivalence and food effect are not anticipated.

8.1.5. 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.

8.1.5.1. Statistical Methodology Specification

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

Endpoint / Variables
Derived PK parameters of DTG: • $AUC_{(0-t)}$ • $AUC_{(0-inf)}$ • C_{max}
Model Specification
• To evaluate the relative bioavailability of equivalent doses of single dose prototype liquid formulations containing 10mg equivalent DTG (Prototypes A and B) compared to a single dose of 2 x 5mg dispersible DTG tablet dispersed in water (DTG Reference Treatment), the PK parameters will be analysed using a mixed effect model as described below: $\log_e$ (PK parameter) = $\beta_0 + \gamma_i + \tau_j + \varepsilon_{ij}$ where, β_0: intercept γ_i: random effect for i^{th} participant, following $N(0, \sigma_b^2)$ τ_j: treatment effect (j = Prototype A or Prototype B or DTG Reference Treatment) ε_{ij}: random error for participant i, treatment effect j, following $N(0, \sigma_w^2)$. • The model parameters will be estimated using Restricted Maximum Likelihood with the Newton-Raphson algorithm. • The Kenward-Roger degree of freedom approach will be used. • Given the random effect for subject "i", the random error is assumed to be independently distributed within the subject. • The least square means for each treatment formulation (Prototype A, Prototype B and DTG Reference Treatment) will be estimated based on the fitted model. The mean difference between the treatment formulations (Prototype A vs. DTG Reference Treatment, and Prototype B vs. DTG Reference Treatment) and its 90% CIs will be also estimated using the within-subject variance. • The estimates of least square means for each treatment formulation, the treatment difference between treatment formulations and the 90% CIs will be exponentially back-transformed to obtain the estimates of geometric means of $AUC_{(0-t)}$, $AUC_{(0-inf)}$ and C_{max} for each treatment

formulation, the ratio of geometric means (Prototype A/DTG Reference, Prototype B/DTG Reference) and its 90% CIs, respectively.

- Within-subject variability (%CVw) for the PK parameters will be estimated using within-subject variance from the analysis model as follows:

$$\%CVw\ (\%) = [\exp(\sigma_w^2) - 1]^{1/2} \times 100$$

Model Checking & Diagnostics

In case there is a problem with model convergence, the arithmetic means for $\log_e$-transformed $AUC_{(0-t)}$ and C_{max} and the treatment differences (Prototype A vs. DTG Reference, Prototype B vs. DTG Reference) within each participant will be calculated using only data from the participants who have completed both the periods for Prototype A and DTG Reference (and Prototype B and DTG Reference, for the second comparison).The mean treatment difference and paired-t test based 90% CIs for treatment difference in $\log_e$ scale will be estimated. The results will be provided in an exponentially back-transformed scale.

Model Results Presentation

Based on the relative bioavailability, the bioequivalence between Prototypes A, B and DTG Reference Treatment will be evaluated as follows:

- The bioequivalence is established when the 90% CI of the ratio for $AUC_{(0-t)}$, $AUC_{(0-inf)}$ and C_{max} between treatment formulations (Prototype A vs. DTG Reference Treatment, and Prototype B vs. DTG Reference Treatment) are within the range of 0.80 to 1.25.
- Even if the 90% CI doesn't meet the above criteria, the bioequivalence is established when the point estimate of the ratio for $AUC_{(0-t)}$, $AUC_{(0-inf)}$ and C_{max} between treatment formulations are within the range of 0.90 to 1.11.

8.1.6. Details of Planned Pharmacokinetic Displays

Analysis of relative bioavailability of Prototypes A and B vs. DTG Reference Treatment for $AUC_{(0-t)}$, $AUC_{(0-inf)}$ and C_{max}

The analysis results will be presented as described in Section 8.1.5.1 - Model Results Presentation.

8.2. Secondary Pharmacokinetic Analyses

8.2.1. Endpoint / Variables

8.2.1.1. Drug Concentration Measures

Refer to Appendix 4: Data Display Standards & Handling Conventions (Section 10.4.3 Reporting Standards for Pharmacokinetic)

8.2.1.2. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters of DTG 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
$AUC_{(0-t)}$ (h*ng/mL)	The area under the concentration-time curve from zero time (pre-dose) to the time of last quantifiable concentration (AUC(0-t)) will be calculated by a combination of linear and logarithmic trapezoidal methods. The linear trapezoidal method will be employed for all incremental trapezoids arising from increasing concentrations and the logarithmic trapezoidal method will be used for those arising from decreasing concentrations (i.e., Linear Up/Log Down calculation method in Phoenix WinNonlin Professional).
$AUC_{(0-inf)}$ (h*ng/mL)	The area under the concentration-time curve from zero time (pre-dose) extrapolated to infinite time ($AUC_{(0-inf)}$) will be calculated as follows: $AUC_{(0-inf)} = AUC_{(0-t)} + C_t / \lambda_z$
$AUC_{(0-24)}$ (h*ng/mL)	The area under the concentration-time curve from zero time (pre-dose) to 24 hours post-dose.
$AUC_{(0-72)}$ (h*ng/mL)	The area under the concentration-time curve from zero time (pre-dose) to 72 hours post-dose.
C_{max} (ng/mL)	Maximum observed plasma concentration following each dose will be obtained directly from the concentration-time data.
C_{24} (ng/mL)	The observed concentration at 24h post-dose.
C_t (ng/mL)	The last observed quantifiable concentration.
t_{max} (h)	The time to maximum observed plasma drug concentration following each dose will be obtained directly from the concentration-time data.
$t_{1/2}$ (h)	Terminal half-life will be calculated as follows: $t_{1/2} = \ln 2 / \lambda_z$
t_{lag} (h)	Absorption lag time.
t (h)	The time of last quantifiable concentration.
%AUCex (%)	The percentage of $AUC_{(0-inf)}$ obtained by extrapolation (%AUCex) will be calculated as follows: $\%AUCex = (AUC_{(0-inf)} - AUC_{(0-t)}) / AUC_{(0-inf)} \times 100$
CL/F (mL/h)	Apparent clearance following oral dosing will be calculated as follows: $CL/F = Dose / AUC_{(0-inf)}$
Vz/F (mL)	Apparent volume of distribution after oral administration will be calculated as follows: $Vz/F = Dose / (\lambda_z \times AUC_{(0-inf)})$
λ_z (/h)	The first order rate constant associated with the terminal (log-linear) portion of the curve.

NOTES:

- Additional parameters may be included as required.

8.2.2. Summary Measure

Descriptive summaries of the above defined parameters except t_{max} will be presented. Unless stated otherwise, descriptive summaries for continuous variables will include n, mean, standard deviation (SD), median, minimum, maximum; whereas, n and percent will be used as summary statistics for categorical variable. Geometric mean with

associated 95% CI, and the between-subject coefficient of variance (CV) (%CVb) for the geometric mean will be included for PK variables, where applicable.

For the t_{max}, point estimates and associated 90% confidence intervals for the median differences between treatment formulations (Prototype A, Prototype B) and DTG Reference Treatment will be presented.

8.2.3. Population of Interest

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

8.2.4. Strategy for Intercurrent (Post-Randomization) Events

Intercurrent events which may affect the evaluation of bioequivalence and food effect are not anticipated.

8.2.5. 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 8.2.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

8.2.5.1. Statistical Methodology Specification

Endpoint / Variables
• t_{max}
Model Specification
• A non-parametric analysis of this endpoint will be performed by using Wilcoxon matched pair test.
Model Results Presentation
• Point estimates and associated 90% confidence intervals for the median differences between treatment formulations (Prototypes A and B) and DTG Reference Treatment will be presented.

8.2.6. Details of Planned Pharmacokinetic Displays

Summaries will be provided by treatment formulations (Prototype A, Prototype B and DTG Reference Treatment), unless otherwise specified.

DTG Plasma Concentration-Time Data

DTG plasma concentrations at every scheduled time point will be summarized using n, mean, standard deviation, median, minimum, and maximum.

Derived DTG Plasma Pharmacokinetic Parameters (non-transformed)

DTG plasma pharmacokinetic parameters defined in Section 8.2.1 will be summarized using n, mean, 95% CI, standard deviation, median, minimum, and maximum.

Derived DTG Plasma Pharmacokinetic Parameters (log-transformed)

For each pharmacokinetic parameter with a log-normal distribution ($AUC_{(0-t)}$, $AUC_{(0-inf)}$, C_{max}, $t_{1/2}$, %AUCex, CL/F, Vz/F, λ_z), the log-transformed parameters will be summarized using n, geometric mean, 95% CI of geometric mean, standard deviation of log-transformed data and between subject coefficient of variation (%CVb).

Non-Parametric Analysis of the Pharmacokinetic Parameter t_{max}

For t_{max}, point estimates of the treatment differences in median along with its 90% CI will be presented. Also, the individual estimates of median of each treatment formulations (Prototypes A and B) and DTG Reference Treatment will be presented along with the n of each group.

9. REFERENCES

GlaxoSmithKline Document Number 2018N379348_01 Study ID 209354. A non-randomized, sequential, fixed-sequence evaluation of prototype dolutegravir liquid formulations versus 5mg dolutegravir dispersible tablets following single-dose fasted-state administrations to normal healthy adult participants. 2019.

10. APPENDICES

10.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

Not applicable, as there is no Per Protocol Population defined for this study.

10.2. Appendix 2: Schedule of Activities

10.2.1. Protocol Defined Schedule of Events

10.2.1.1. Screening Assessments

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

BMI: Body mass index, ECG: Electrocardiogram, hCG: Human chorionic gonadotropin, FSH: Follicle stimulating hormone; HIV: Human immunodeficiency virus, Hep B: Hepatitis B; Hep C: Hepatitis C

10.2.1.2. Treatment Period Assessments

Assessments	All Dosing Periods							Follow-up	Notes
		Day 1			Day 2	Day 3	Day 4		
	Day -1	Pre-dose	0 hr	Post Dose	-	48 hr	72 hr		
Admission to Unit	X								
Discharge						X			
Outpatient Visit							X	X	*Follow-up visit will occur 7 to 14days post last dose.*
12-lead ECG	X								*Single ECGs will be collected at Screening and on Day-1 of Period 1 only. Additional ECGs may be performed at the discretion of the investigator.*
Vital signs	X						X	X	*Single measurements performed at all time points.*
Brief Physical Exam	X								• *Brief examinations may be made full examinations and laboratory procedures may be repeated, if needed, at the discretion of the Investigator.*
Urine Drug / Cotinine and Breathalyzer	X								• *Illicit Drug/Alcohol/Cotinine screening will be performed in accordance with the sites' standard practice.*
Clinical laboratory tests	X							X*	• *Clinical laboratory tests – see Table 6 of Study Protocol.* • **Clinical laboratory tests at follow-up are only necessary if participant had a previous abnormal lab value*
Dosing			**X**						*Participant will be dosed while in the seated position.*
Meals	X			Post 4-hour PK sample	Per standard at the clinic				*Participants will fast from 10hrs pre-dose to 4-hours post-dose.*
Pharmacokinetic Sampling		X		Collect at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, and 48-hours post-dose			X		• *Pre-dose (within 15 minutes prior to dosing).* • *4-hour post dose sample must be taken prior to provision of food.* • *Permitted window for the collection of PK sample at each time point is specified in Section 8.5.1. of Study Protocol.*
Adverse Events/SAEs	X	←==========X==========→						X	
Concomitant medications	X	←==========X==========→						X	

10.3. Appendix 3: Study Phases and Treatment Emergent Adverse Events

10.3.1. Study Phases

Assessments and events (e.g., study withdrawal) will be classified according to the time of occurrence relative to dosing start Date and Time by Period.

Study Phase	Definition
Pre-Treatment	Reference Day ≤ Previous Day of Dosing Start Date in Period 1
Period 1	Previous Day of Dosing Start Date in Period 1 < Reference Day ≤ Previous Day of Dosing Start Date in Period 2
Period 2	Previous Day of Dosing Start Date in Period 2 < Reference Day ≤ Previous Day of Dosing Start Date in Period 3
Period 3	Previous Day of Dosing Start Date in Period 3 < Reference Day ≤ Dosing Start Date in Period 3 + 4 Days
Post-Treatment	Reference Day > Dosing Start Date in Period 3 + 4 Days

10.3.1.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is before 7 days prior to screening visit
Concomitant	Any medication that is not a prior

NOTES:

- Please refer to Appendix 6: Reporting Standards for Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.

10.3.2. Treatment Emergent Flag for Adverse Events

Study Phase	Definition
Pre-Treatment	AE Onset Date and Time < Study First Dosing Start Date and Time
Period 1	Study First Dosing Start Date and Time ≤ AE Onset Date and Time < Dosing Start Date and Time in Period 2
Period 2	Dosing Start Date and Time in Period 2 ≤ AE Onset Date and Time < Dosing Start Date and Time in Period 3
Period 3	Dosing Start Date and Time in Period 3 ≤ AE Onset Date and Time ≤ Dosing Start Date and Time in Period 3 + 4 Days
Post-Treatment	AE Onset Date and Time > Dosing Start Date in Period 3 + 4 Days
Time since Study First Dose (min)	If study phase of the event is pre-treatment, AE Onset Date and Time - Study First Dosing Start Date and Time otherwise AE Onset Date and Time – Study First Dosing Start Date and Time + 1 min
Time since Period First Dose (min)	If study phase of the AE is Pre-Treatment, set to missing If study phase of the AE is Period 1, AE Onset Date and Time – Dosing Start Date and Time in Period 1 + 1 min If study phase of the AE is Period 2, AE Onset Date and Time – Dosing Start Date and Time in Period 2 + 1 min If study phase of the AE is Period 3, AE Onset Date and Time – Dosing Start Date and Time in Period 3 + 1 min If study phase of the AE is Post-Treatment, AE Onset Date and Time – (Dosing Start Date in Period 3 + 4 Days) + 1 min
Duration (min)	AE Resolution Date and Time – AE Onset Date and Time + 1 min
Drug-related	If relationship is marked 'YES' on eCRF or value is missing.

NOTES:

- If the study treatment stop date is missing, then the AE will be considered to be treatment emergent.
- Time of study treatment dosing and start/stop time of AEs should be considered, if collected.

10.4. Appendix 4: Data Display Standards & Handling Conventions

10.4.1. Reporting Process

Software	
• The currently supported versions of SAS software 9.4 will be used.	
Reporting Area	
HARP Server	: US1SALX00259
HARP Compound	: \ARPROD\GSK1349572\MID209354\
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards (SDTM IG Version 3.2 & ADaM IG Version 1.1].	
Generation of RTF Files	
• RTF files will be generated.	

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 GUI_51487 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 Programmer	No PK parameters derived by programmer are planned
Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	Yes, refer to Standards for Handling NQ Impacted PK Parameters in GUI_51487.
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards: Standards for the Transfer and Reporting of PK Data using HARP

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

Period Day

• Calculated as the number of days from Dosing Date in Period 1 or Period 2 or Period 3.
  • If Study Phase of Ref Assessment or Event = Pre-Treatment or Missing
  → Period Day = Missing
  • If Study Phase of Ref Assessment or Event = Period 1
  → If Ref Date is on or after Dosing Date in Period 1, Period Day = Ref Date – Dosing Date in Period 1 + 1 day
  • If Study Phase of Ref Assessment or Event = Period 2
  → If Ref Date is on or after Dosing Date in Period 2, Period Day = Ref Date – Dosing Date in Period 2 + 1 day
  • If Study Phase of Ref Assessment or Event = Period 3
  → If Ref Date is on or after Dosing Date in Period 3, Period Day = Ref Date – Dosing Date in Period 2 + 1 day
  • If Study Phase of Ref Assessment or Event = Post-Treatment
  → If Ref Date is after Dosing Date in Period 3 + 4 Days, Period Day = Ref Date – (Dosing Date in Period 3 + 4 Days) + 1 day

10.5.2. Study Population

Extent of Exposure
• Number of days of exposure to study drug for each period will be calculated based on the formula: **Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1** • Participants who were enrolled but did not report a treatment start date will be categorised as having zero days of exposure.
Age
• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows: ○ A date and month will be imputed as '30th June' as it will not be captured. • Date of Informed Consent will be used as reference date of calculation.

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 completion of 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.

10.6.2. 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: o 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. o 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 and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• The eCRF does not allow 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 will not be missing. • The eCRF allows for the possibility of missing times to be recorded for AE start and end dates. Missing times will be imputed using the following convention: o If the missing time is a start time, a '00:00' will be used for the time. o If the missing time is a stop time, a '23:59' will be used for the time. • The recorded missing time will be displayed in listings without imputed values.
Concomitant Medications/ Medical History	• Partial dates for any concomitant medications recorded in the CRF 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 eCRF allows for the possibility of missing times to be recorded for concomitant medications start and end dates. Missing times will be imputed using the following convention: o If the missing time is a start time, a '00:00' will be used for the time. o If the missing time is a stop time, a '23:59' will be used for the time. • The recorded partial date and missing time will be displayed in listings without imputed values.

10.7. Appendix 7: Values of Potential Clinical Importance

Any DAIDS Grade 2 or above event will be treated as an event of potential clinical importance.

Please refer to the link below for more details:

https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

10.8. Appendix 8: Abbreviations & Trade Marks

10.8.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
A&R	Analysis and Reporting
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
CTC	Common Terminology Criteria for Adverse Events
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DBF	Database Freeze
DBR	Database Release
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
ECG	Electrocardiogram
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
GSK	GlaxoSmithKline
IA	Interim Analysis
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
ITT	Intent-To-Treat
MMRM	Mixed Model Repeated Measures
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
PopPK	Population PK
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System

Abbreviation	Description
SAC	Statistical Analysis Complete
SDSP	Study Data Standardization Plan
SDTM	Study Data Tabulation Model
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings
TMF	Trial Master File

10.8.2. Trademarks

Trademarks of the ViiV Healthcare Group of Companies
None

Trademarks not owned by the ViiV Healthcare 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 1.12	Not Applicable
Safety	3.1 to 3.21	Not Applicable
Pharmacokinetic	4.1 to 4.5	4.1 to 4.5
Section	**Listings**	
ICH Listings	1 to 33	

10.9.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 10: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Pharmacokinetic	PK_Fn	PK_Tn	Not Applicable

NOTES:

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

10.9.3. Deliverables

Delivery	Description
SAC	Final Statistical Analysis Complete

10.9.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	All Participants	ES1A	Summary of Participant Disposition for the Participant Conclusion Record	Only "Total" column will appear Please refer to mock shell DM1 in Appendix 10 for an idea of how a typical study population display would look like.	SAC
1.2.	All Participants	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment	Only "Total" column will appear	SAC
1.3.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure	Only "Total" column will appear	SAC
1.4.	Enrolled	NS1	Summary of Number of Participant by Country and Site ID	Only "Total" column will appear	SAC
Protocol Deviation					
1.5.	All Participants	DV1	Summary of Important Protocol Deviations	Only "Total" column will appear	SAC
Population Analysed					
1.6.	Enrolled	SP1	Summary of Study Populations		SAC
Demographic and Baseline Characteristics					
1.7.	All Participants	DM3	Summary of Demographic Characteristics	Only "Total" column will appear	SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.8.	Enrolled	DM11	Summary of Age Ranges	Only "Total" column will appear	SAC
1.9.	All Participants	DM5	Summary of Race and Racial Combinations	Only "Total" column will appear	SAC
Prior and Concomitant Medications					
1.10.	All Participants	MH1	Summary of Past Medical Conditions	Only "Total" column will appear	SAC
1.11.	All Participants	MH1	Summary of Current Medical Conditions	Only "Total" column will appear	SAC
1.12.	All Participants	CM1	Summary of Concomitant Medications	Only "Total" column will appear	SAC

10.9.5. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
3.1.	All Participants	AE1CP	Summary of All Adverse Events by System Organ Class and Preferred Term	Include "Total" column Please refer to mock shell AE1CP in Appendix 10 for an idea of how a typical safety display would look like.	SAC
3.2.	All Participants	AE5B	Summary of All Adverse Events by Maximum Grade by System Organ Class and Preferred Term	Include "Total" column	SAC
3.3.	All Participants	AE3	Summary of Common (>=5%) Adverse Events by Overall Frequency	Include "Total" column	SAC
3.4.	All Participants	AE3	Summary of Common (>=5%) Grade 2-4 Adverse Events by Overall Frequency	Include "Total" column	SAC
3.5.	All Participants	AE1CP	Summary All Drug-Related Adverse Events by System Organ Class and Preferred Term	Include "Total" column	SAC
3.6.	All Participants	AE5B	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term and Maximum Grade	Include "Total" column	SAC
3.7.	All Participants	AE15	Summary of Common (>=5%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Participant and Occurrences)	Include "Total" column	SAC
3.8.	All Participants	AE3	Summary of Common (>=5%) Drug-Related Grade 2-4 Adverse Events by Overall Frequency	Include "Total" column	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Serious and Other Significant Adverse Events					
3.9.	All Participants	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)	Include "Total" column	SAC
Laboratory: Chemistry					
3.10.	All Participants	LB1	Summary of Chemistry Changes from Baseline	Include "Total" column	SAC
3.11.	All Participants	LB17	Summary of Worst Case Chemistry Results by PCI Criteria Post-Baseline Relative to Baseline	Include "Total" column	SAC
3.12.	All Participants	LB16	Summary of Worst Case Chemistry Results by Maximum Grade Increase Post-Baseline Relative to Baseline	Include "Total" column	SAC
Laboratory: Hematology					
3.13.	All Participants	LB1	Summary of Hematology Changes from Baseline	Include "Total" column	SAC
3.14.	All Participants	LB17	Summary of Worst Case Hematology Results by PCI Criteria Post-Baseline Relative to Baseline	Include "Total" column	SAC
3.15.	All Participants	LB16	Summary of Worst Case Hematology Results by Maximum Grade Increase Post-Baseline Relative to Baseline	Include "Total" column	SAC
Laboratory: Urinalysis					
3.16.	All Participants	LB1	Summary of Urine Concentration Changes from Baseline	Include "Total" column	SAC
3.17.	All Participants	UR1	Summary of Worst Case Urinalysis Results (Discrete or Character Values) Post-Baseline Relative to Baseline	Include "Total" column	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory: Hepatobiliary (Liver)					
3.18.	All Participants	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting	Include "Total" column	SAC
3.19.	All Participants	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities	Include "Total" column	SAC
Vital Signs					
3.20.	All Participants	VS1	Summary of Change from Baseline in Vital Signs	Only "Total" column will appear	SAC
3.21.	All Participants	VS3	Summary of Worst Case Vital Signs Results by Maximum Grade Increase Post-Baseline Relative to Baseline	Only "Total" column will appear	SAC

10.9.6. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.1.	PK	PK01	Summary of DTG Plasma Concentration-Time Data		SAC
4.2.	PK	PK03	Summary of Derived DTG Plasma Pharmacokinetic Parameters (non-transformed)		SAC
4.3.	PK	PK05	Summary of Derived DTG Plasma Pharmacokinetic Parameters (log-transformed)		SAC
4.4.	PK	PK_T1	Non-parametric Analysis of tmax	Refer to example shell	SAC
4.5.	PK	PK_T2	Analysis of Relative Bioavailability of Prototype Formulations vs. DTG Reference Treatment for Cmax, AUC(0-t), and AUC(0-inf)	Refer to example shell	SAC

10.9.7. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.1.	PK	PK16b	Individual DTG Plasma Concentration-Time Plots by Participant	A graph on linear and semi-logarithmic scales will be produced.	SAC
4.2.	PK	PK16b	Individual DTG Plasma Concentration-Time Plots by Treatment	A graph on linear and semi-logarithmic scales will be produced.	SAC
4.3.	PK	PK17	Mean (+SD) DTG Plasma Concentration-Time Plots	A graph on linear and semi-logarithmic scales will be produced.	SAC
4.4.	PK	PK18	Median DTG Plasma Concentration-Time Plots	A graph on linear and semi-logarithmic scales will be produced.	SAC
4.5.	PK	PK_F1	Plot of Individual DTG Plasma Cmax, AUC(0-t), and AUC(0-inf) by Treatment	Refer to example shell	SAC

10.9.8. 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	Journal Guidelines	SAC
2.	All Participants	ES3	Listing of Reasons for Study Withdrawal	ICH E3	SAC
3.	All Participants	SD3	Listing of Reasons for Study Treatment Discontinuation	ICH E3	SAC
4.	All Participants	TA2	Listing of Planned and Actual Treatments	IDSL	SAC
Protocol Deviations					
5.	All Participants	DV2A	Listing of Important Protocol Deviations	ICH E3	SAC
6.	All Participants	IE4	Listing of Participants with Inclusion/Exclusion Criteria Deviations	ICH E3	SAC
Populations Analysed					
7.	All Participants	SP3a	Listing of Participants Excluded from Any Population	ICH E3	SAC
Demographic and Baseline Characteristics					
8.	All Participants	DM4	Listing of Demographic Characteristics	ICH E3	SAC
9.	All Participants	DM10	Listing of Race	ICH E3	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Prior and Concomitant Medications					
10.	All Participants	CM5	Listing of Concomitant Medications	IDSL	SAC
Exposure and Treatment Compliance					
11.	All Participants	EX4	Listing of Exposure Data	ICH E3	SAC
Adverse Events					
12.	All Participants	AE9CP	Listing of All Adverse Events	ICH E3	SAC
13.	All Participants	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH E3	SAC
14.	All Participants	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text	IDSL	SAC
Serious and Other Significant Adverse Events					
15.	All Participants	AE9CPa	Listing of Fatal Serious Adverse Events	ICH E3	SAC
16.	All Participants	AE9CPa	Listing of Non-Fatal Serious Adverse Events	ICH E3	SAC
17.	All Participants	AE14	Listing of Reasons for Considering as a Serious Adverse Event	ICH E3	SAC
18.	All Participants	AE9CP	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	ICH E3	SAC
19.	All Participants	AE8 / AECP8 / AE9 / AE9CP	Listing of Other Significant Adverse Events	ICH E3	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Hepatobiliary (Liver)					
20.	All Participants	MH3	Listing of Medical Conditions for Participants with Liver Stopping Events	IDSL	SAC
21.	All Participants	SU2	Listing of Substance Use for Participants with Liver Stopping Events	IDSL	SAC
All Laboratory					
22.	All Participants	LB6	Listing of All Laboratory Data for Participants with Any Value of Potential Clinical Importance	ICH E3	SAC
23.	All Participants	LB6	Listing of Laboratory Values of Potential Clinical Importance		SAC
24.	All Participants	LB14	Listing of Laboratory Data with Character Results	ICH E3	SAC
25.	All Participants	UR2B	Listing of Urinalysis Data for Participants with Any Value of Potential Clinical Importance	ICH E3	SAC
ECG					
26.	All Participants	EG4	Listing of All ECG Values for Participants with Any Value of Potential Clinical Importance	IDSL	SAC
27.	All Participants	EG4	Listing of ECG Values of Potential Clinical Importance	IDSL	SAC
28.	All Participants	EG6	Listing of All ECG Findings for Participants with an Abnormal ECG Finding	IDSL	SAC
29.	All Participants	EG6	Listing of Abnormal ECG Findings	IDSL	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Vital Signs					
30.	All Participants	VS5	Listing of All Vital Signs Data for Participants with Any Value of Potential Clinical Importance	IDSL	SAC
31.	All Participants	VS5	Listing of Vital Signs of Potential Clinical Importance	IDSL	SAC
PK					
32.	All Participants	PK08	Listing of DTG Plasma Pharmacokinetic Concentration-Time Data	IDSL	SAC
33.	All Participants	PK14	Listing of Derived DTG Plasma Pharmacokinetic Parameters	IDSL	SAC

10.10. Appendix 10: Example Mock Shells for Data Displays

Example DM1
Protocol: 209354 Page 1 of 3
Population: All Patients

Table X
Summary of Demographic Characteristics

	Total (N=200)
Sex	
n	200
F	100 (50%)
M	100 (50%)
Age (YEARS)[1]	
n	200
Mean	50.0
SD	10.00
Median	50.0
Min.	18
Max.	65
Age Group(YEARS)[1]	
<=18	5 (3%)
19-64	100 (50%)
>=65	95 (48%)

[1] Age is imputed when full date of birth is not provided.

Example AE1CP

Protocol: 209354
Population: All Patients

Table X
Summary of Adverse Events by System Organ Class and Preferred Term

System Organ Class Preferred Term	Prototype A (N=78)	Prototype B (N=78)	DTG Reference (N=78)	Total (N=78)
ANY EVENT	58 (74%)	64 (82%)	64 (85%)	65 (83%)
Gastrointestinal disorders				
Any event	28 (36%)	34 (44%)	22 (29%)	34 (44%)
Dyspepsia	9 (12%)	11 (14%)	5 (7%)	15 (19%)
Nausea	6 (8%)	8 (10%)	4 (5%)	11 (14%)
Vomiting Nos	3 (4%)	10 (13%)	3 (4%)	10 (13%)
Constipation	6 (8%)	6 (8%)	3 (4%)	7 (9%)
Diarrhoea Nos	2 (3%)	4 (5%)	2 (3%)	6 (8%)
Toothache	3 (4%)	1 (1%)	3 (4%)	5 (6%)
Abdominal Pain Upper	1 (1%)	2 (3%)	2 (3%)	5 (6%)
Dry Mouth	0	1 (1%)	4 (5%)	5 (6%)
Flatulence	1 (1%)	3 (4%)	1 (1%)	4 (5%)
Gastrointestinal Upset	0	1 (1%)	3 (4%)	3 (4%)
Haemorrhoids	3 (4%)	0	0	3 (4%)
Salivary Hypersecretion	0	2 (3%)	1 (1%)	2 (3%)
Abdominal Tenderness	0	2 (3%)	0	2 (3%)
Hyperacidity	0	1 (1%)	1 (1%)	2 (3%)
Loose Stools	0	2 (3%)	0	2 (3%)
Abdominal Pain Nos	1 (1%)	0	0	1 (1%)
Faecal Incontinence	0	1 (1%)	0	1 (1%)
Gastritis Nos	0	1 (1%)	0	1 (1%)
Lip Disorder Nos	0	0	1 (1%)	1 (1%)
Lip Dry	0	0	1 (1%)	1 (1%)
Stomach Discomfort	0	0	1 (1%)	1 (1%)
Nervous system disorders				
Any event	28 (36%)	28 (36%)	27 (36%)	30 (38%)
Headache	15 (19%)	11 (14%)	14 (19%)	27 (35%)
Dizziness	3 (4%)	8 (10%)	3 (4%)	11 (14%)
Extrapyramidal Disorder	4 (5%)	4 (5%)	5 (7%)	10 (13%)

Example: PK_T1 Page 1 of n
Protocol: 209354
Population: PK

Table X
Analysis of Relative Bioavailability of Prototype Formulations vs. DTG Reference Treatment for Cmax, AUC(0-t), and AUC(0-inf)

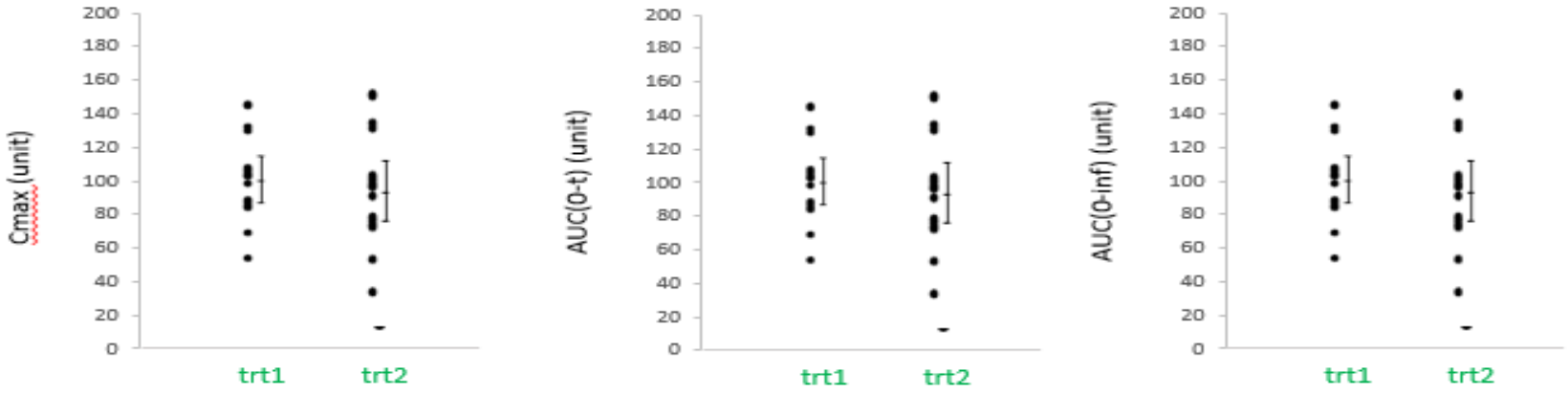
Parameter	Treatment Comparison	Adjusted Geom Mean				Ratio (trt2/trt1)	90% CI	%CVw[1]
		n	Test	n	Ref			
Cmax (unit)	trt1 vs ref	xx	xx.xxx	xx	xx.xxx	x.xxx	(x.xxx, x.xxx)	x.xxx
	trt2 vs ref	xx	xx.xxx	xx	xx.xxx	x.xxx	(x.xxx, x.xxx)	x.xxx
AUC(0-t)(unit)	trt1 vs ref	xx	xx.xxx	xx	xx.xxx	x.xxx	(x.xxx, x.xxx)	x.xxx
	trt2 vs ref	xx	xx.xxx	xx	xx.xxx	x.xxx	(x.xxx, x.xxx)	x.xxx
AUC(0-inf) (unit)	trt1 vs ref	xx	xx.xxx	xx	xx.xxx	x.xxx	(x.xxx, x.xxx)	x.xxx
	trt2 vs ref	xx	xx.xxx	xx	xx.xxx	x.xxx	(x.xxx, x.xxx)	x.xxx

[1] Within-subject variability of each PK parameter

trt1 = “Prototype A”, trt2 = “Prototype B” trt3 = “DTG Reference”

Example: PK_F1
Protocol: 209354
Population: PK

Table X
Plot of Individual DTG Plasma Cmax, AUC(0-t), and AUC(0-inf) by Treatment



Note: Geometric mean and 95% CI

Programming notes:
Add three treatments – trt1 = "Prototype A", trt2 = "Prototype B" trt3 = "DTG Reference"
Figures will be presented in left (Cmax), center (AUC(0-t), and right (AUC(0-inf).