TITLE PAGE

Protocol Title: 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

Protocol Number: 209354 / 1

Compound Number: GSK1349572

Study Phase: Phase 1

Short Title: Dolutegravir Paediatric Liquid Formulation Study

Sponsor Name and Legal Registered Address: (excluding US):
ViiV Healthcare UK Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

US IND Sponsor Name and Legal Registered Address:
ViiV Healthcare Company
Five Moore Drive
P.O. 13398
Research Triangle Park, NC 27709-3398, USA
Telephone: PPD

Medical Monitor Name and Contact Information
PPD FCP, MSc
Director, Clinical Development Research and Development, ViiV Healthcare
980 Great West Road
Brentford, Middlesex, TW 9GS United Kingdom
PPD
PPD

Regulatory Agency Identifying Number(s): EudraCT - 2018-003613-18

Approval Date: 27-FEB-2019

In some countries, local law requires that the Clinical Trial sponsor is a local company legal entity. In these instances, the appropriate company to be identified as Sponsor must be agreed with the global ViiV Healthcare clinical team and signed off by the Vice President, Global Medical Strategy

This study is sponsored by ViiV Healthcare. GlaxoSmithKline and Quotient Clinical are supporting ViiV Healthcare in the conduct of this study.

SPONSOR SIGNATORY:

PPD

PPD PPD PPD PPD PPD PPD

Kimberly Y. Sm MD, MPH
Vice President, C rategy
ViiV Healthcare

2/27/19
Date

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 1	*27-FEB-2019*	2018N379348_01
Original Protocol	*29-OCT-2018*	2018N379348_00

Amendment 01 27-February-2019

Overall Rationale for the Amendment: 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.

The US IND number was removed from the cover page as this study will be conducted in the UK.

Some additional copy changes may have been made to text (e.g., Table 3, changed formulation from 1 and 2, to A and B). These were administrative change not affecting participants.

Section # and Name	**Description of Change**	**Brief Rationale**
Cover Page	IND number removed	The study is not occurring in the United States, the presence of an IND number is not warranted.
Section 1.1 - Synopsis, Section 1.2 - Schema, Section 1.3-Schedule of Activities, Table 2 Section 2 - Introduction, Section 4.1 – Overall Design, Section 4.2 – Formulation Decision, Section 4.4 – Justification for Dose, Section 6.1 – Study Intervention(s) Administered, Section 7 – Discontinuation of Study Intervention, Section 9.1 – Statistical Hypothesis, Section 9.4.1 – Primary and Secondary Analyses, Section 9.5 – Preliminary Analyses	All changes were made to reflect the reduction in study design from up to 5 to only 2 test formulations, including, but not limited to, the removal of a need for interim dosing reviews as these will no longer be necessary.	Pre-clinical testing yielded only 2 prototypes suitable to take forward clinically into this study. These changes reflect the reduction in study design from up to 5 to only 2 test formulations.

TABLE OF CONTENTS

PAGE

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE 3

1. PROTOCOL SUMMARY 7
   - 1.1. Synopsis 7
   - 1.2. Schema 8
   - 1.3. Schedule of Activities (SoA) 9

2. INTRODUCTION 11
   - 2.1. Study Rationale 11
   - 2.2. Background 11
   - 2.3. Benefit/Risk Assessment 12
     - 2.3.1. Risk Assessment 13
     - 2.3.2. Benefit Assessment 15
     - 2.3.3. Overall Benefit: Risk Conclusion 15

3. OBJECTIVES AND ENDPOINTS 16

4. STUDY DESIGN 16
   - 4.1. Overall Design 16
   - 4.2. Formulation Decision 17
   - 4.3. Scientific Rationale for Study Design 18
   - 4.4. Justification for Dose 18
   - 4.5. Discontinuation / Stopping Study 18
   - 4.6. End of Study Definition 19

5. STUDY POPULATION 19
   - 5.1. Inclusion Criteria 19
   - 5.2. Exclusion Criteria 20
   - 5.3. Lifestyle Considerations 22
     - 5.3.1. Meals and Dietary Restrictions 22
       - 5.3.1.1. Fasting Conditions 22
       - 5.3.1.2. Fed Conditions 22
     - 5.3.2. Caffeine, Alcohol, and Tobacco 22
     - 5.3.3. Activity 23
   - 5.4. Screen Failures 23

6. STUDY INTERVENTION 23
   - 6.1. Study Intervention(s) Administered 24
   - 6.2. Preparation/Handling/Storage/Accountability 25
   - 6.3. Measures to Minimize Bias: Randomization and Blinding 25
   - 6.4. Study Intervention Compliance 25
   - 6.5. Concomitant Therapy 25
   - 6.6. Dose Modification 26
   - 6.7. Intervention after the End of the Study 26

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 26
   - 7.1. Discontinuation of Study Intervention 26

7.1.1. Liver Chemistry Stopping Criteria 27
7.1.2. QTc Stopping Criteria 28
7.1.3. Temporary Discontinuation 28
7.1.4. Study Termination 28
7.2. Participant Discontinuation/Withdrawal from the Study 29
7.3. Lost to Follow Up 29

8. STUDY ASSESSMENTS AND PROCEDURES 30
8.1. Efficacy Assessments 31
8.2. Safety Assessments 31
8.2.1. Physical Examinations 31
8.2.2. Vital Signs 31
8.2.3. Electrocardiograms 32
8.2.4. Clinical Safety Laboratory Assessments 32
8.3. Adverse Events and Serious Adverse Events 33
8.3.1. Time Period and Frequency for Collecting AE and SAE Information 33
8.3.2. Method of Detecting AEs and SAEs 33
8.3.3. Follow-up of AEs and SAEs 34
8.3.4. Regulatory Reporting Requirements for SAEs 34
8.3.5. Pregnancy 34
8.4. Treatment of Overdose 34
8.5. Pharmacokinetics 35
8.5.1. Blood Sample Collection 35
8.5.2. Sample Processing Procedures 35
8.5.3. Sample Storage Conditions 36
8.5.4. Sample Analysis 36
8.6. Pharmacodynamics 36
8.7. Genetics 36
8.8. Biomarkers 36
8.9. Medical Resource Utilization and Health Economics 36

9. STATISTICAL CONSIDERATIONS 37
9.1. Statistical Hypotheses 37
9.2. Sample Size Determination 37
9.2.1. Sample Size Assumptions 37
9.2.2. Sample Size Sensitivity 37
9.3. Populations for Analyses 38
9.4. Statistical Analyses 38
9.4.1. Primary and Secondary Analyses 39
9.4.2. Pharmacokinetic Analyses 39
9.4.3. Safety Analyses 40
9.5. Preliminary Analyses 40

10. REFERENCES 41

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 42
11.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 42
11.1.1. Regulatory and Ethical Considerations 42
11.1.2. Protocol Amendments 42

11.1.3. Protocol Deviations 43
11.1.4. Financial Disclosure 43
11.1.5. Informed Consent Process 43
11.1.6. Data Protection 44
11.1.7. Publication Policy 44
11.1.8. Dissemination of Clinical Study Data 44
11.1.9. Data Quality Assurance 45
11.1.10. Source Documents 45
11.1.11. Study and Site Closure 46
11.1.12. Publication Policy 46
11.2. Appendix 2: Clinical Laboratory Tests 47
11.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 48
11.3.1. Definition of AE 48
11.3.2. Definition of SAE 49
11.3.3. Recording and Follow-Up of AE and SAE 50
11.3.4. Reporting of SAE to ViiV Healthcare/GSK 52
11.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information 53
11.4.1. Definitions: 53
11.4.2. Collection of Pregnancy Information: 53
11.5. Appendix 5: Division of AIDS Table For Grading The Severity Of Adult And Paediatric Averse Events Version 2.1, March 2017 55
11.6. Appendix 6: Toxicity Management 56
11.6.1. ANEMIA 56
11.6.2. TOTAL BILIRUBIN ELEVATION 57
11.6.3. AST AND ALT ELEVATION 57
11.6.4. RASH 57
11.6.5. ALLERGIC REACTION 59
11.6.6. Decline in Renal Function 60
11.7. Appendix 7: Liver Safety: Required Actions and Follow-up Assessments 61
11.8. Appendix 8: Safety Reporting to Ethics Committee and Regulatory Authorities 62
11.9. Appendix 9: Abbreviations and Trademarks 64
11.10. Appendix 10: Protocol Amendment History 67

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: 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

Short Title: Dolutegravir (DTG) Paediatric liquid formulation study

Rationale: Dolutegravir (DTG) has been shown to be safe and effective in adults who are infected with human immunodeficiency virus (HIV). Dosage forms for paediatric patients are in development and under investigation for safety and efficacy. This study will evaluate the pharmacokinetics (PK), via relative bioavailability, of single dose prototype liquid formulations containing 10 mg equivalent DTG compared to 2 x 5mg dispersible DTG tablets dispersed in water. These DTG liquid formulations are being developed to support future efficacy and safety studies for the treatment of HIV-infected new-borns of up to approximately 6 weeks of age.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
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	
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, $t_{½}$, λz, $\%AUC_{ex}$, $AUC_{(0-24)}$, $AUC_{(0-72)}$, CL/F and Vz/F, Ct, and 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
t1/2 = the elimination half-life
CL/F = apparent oral clearance
Vz/F= apparent oral volume of distribution

Overall Design: This is an open-label, single-centre, single dose study in healthy male and female participants to assess prototype liquid formulations containing 10 mg equivalent DTG.

Disclosure Statement: This is an Intervention study with 2 prototype liquid formulations of DTG versus a reference dose of 2 x 5mg dispersible DTG (TIVICAY) tablet dispersed in water.

Number of Participants: A maximum of 18 participants will be enrolled to receive study intervention such that approximately 16 evaluable participants complete the study. An evaluable participant will have completed the planned safety and PK assessments up to 72 hours after dosing. An evaluable participant must also have received the relevant prototype and reference formulations for the comparisons of interest (e.g. a prototype formulation and the reference).

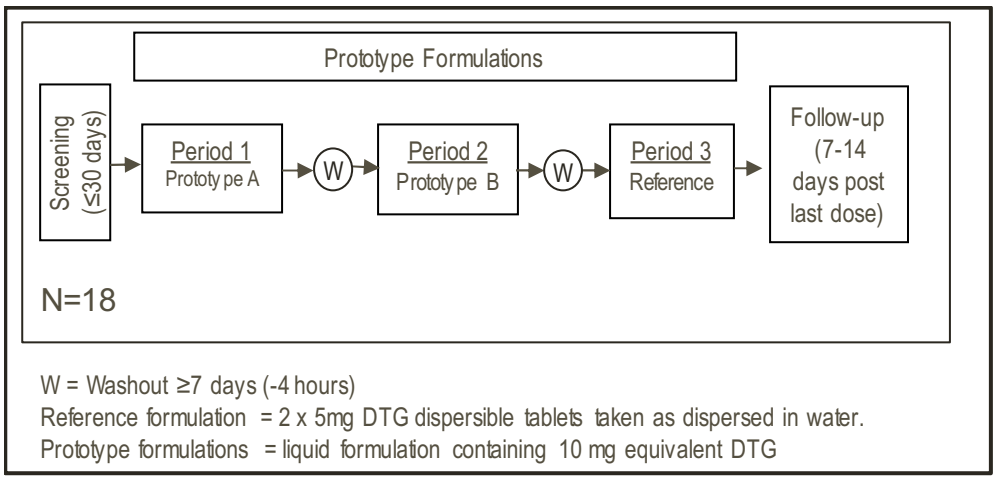
If participants prematurely discontinue the study, additional replacement participants may be recruited at the discretion of the Sponsor in consultation with the investigator.

Intervention Groups and Duration: This is an open-label single dose study, please see the study schema (Figure 1) below.

Data Monitoring Committee: No

1.2. Schema

Figure 1 Study Design Schematic



1.3. Schedule of Activities (SoA)

Table 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

- The timing and number of planned study assessments, including safety or pharmacokinetic assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Any changes in the timing or addition of time points for any planned study assessments as the result of emerging pharmacokinetic data from this study must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment. The Competent Authority (CA) and ethics committee (EC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the CA and the EC before implementation.
- There are times where it is required for more than one procedure to be completed at the same time point. In these instances, the following will apply to post-dose time points:

  PK samples take priority over other procedures scheduled at the same time point. As guidance, the preferred order of assessments is:

  ECGs (if needed) → Vital Signs → PK blood sampling (nominal time) → Other assessments eg physical exams,

- Electrocardiograms (ECGs) will be taken prior to vital signs when both measurements are scheduled at the same time point. Other assessments, e.g. physical examinations etc, will be performed within the required time windows. All safety assessments will be timed and performed relative to the start of dosing.

Table 2 Treatment Period Assessments

Assessments	All Dosing Periods							Follow-up	Notes
	Day -1	Day 1			Day 2	Day 3	Day 4		
		Pre-dose	0 hr	Post Dose	-	48 hr	72 hr		
Admission to Unit	X								
Discharge						X			
Outpatient Visit							X	X	*Follow-up visit will occur 7 to 14 days post last dose.*
12-lead ECG	X								*Single ECGs will be collected at Screening and on Day-1 of Period 1 only. Additional ECGs may be performed at the discretion of the investigator.*
Vital signs	X						X	X	*Single measurements performed at all time points.*
Brief Physical Exam	X								• *Brief examinations may be made full examinations and laboratory procedures may be repeated, if needed, at the discretion of the Investigator.* • *Illicit Drug/Alcohol/Cotinine screening will be performed in accordance with the sites' standard practice.* • *Clinical laboratory tests – see Table 6* • **Clinical laboratory tests at follow-up are only necessary if participant had a previous abnormal lab value*
Urine Drug / Cotinine and Breathalyzer	X								
Clinical laboratory tests	X							X*	
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.*
Adverse Events/SAEs	X	←==========X==========→						X	
Concomitant medications	X	←==========X==========→						X	

- The timing and number of planned study assessments, including safety or PK assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

- Any changes in the timing or addition of time points for any planned study assessments as the result of emerging PK data from this study must be documented and approved by the relevant study team member and then archived in the sponsor and site study files but will not constitute a protocol amendment. The Competent Authority (CA) and ethics committee (EC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the CA and the EC before implementation.

2. INTRODUCTION

The purpose of the present study is to evaluate the relative bioavailability of two prototype liquid formulations containing 10 mg equivalent DTG in healthy adult participants versus single doses of 2 x 5 mg dispersible tablets dispersed in water.

2.1. Study Rationale

Dolutegravir (DTG) has been shown to be safe and effective in adults who are infected with HIV. Dosage forms for paediatric patients are in development and under investigation for safety and efficacy. This study will evaluate the pharmacokinetics, via relative bioavailability, of single dose prototype liquid formulations containing 10 mg equivalent DTG compared to 5mg dispersible DTG tablets dispersed in water. These DTG liquid formulations are being developed to support future efficacy and safety studies for the treatment of HIV-infected new-borns of up to approximately 6 weeks of age.

2.2. Background

The safety and efficacy of DTG (TIVICAY) is already established in adults. For younger children aged ≥4 weeks to <12 years of age, the evaluation of once daily dosing of DTG will be supported by data from paediatric efficacy and safety studies of DTG alone and in combination with 2 nucleoside reverse transcriptase inhibitors (NRTIs; lamivudine and abacavir) and current labelling for the individual components of the FDC in paediatric patients. It is the Sponsor's intention to develop both a dispersible tablet (DT) paediatric formulation of DTG and a liquid formulation of DTG that would optimize the dose through achieving drug exposures similar to that of approved adult formulations. Under the assumption that these paediatric formulations are feasible, the DTG PK data from this study in healthy adult participants will be compared to drug exposures obtained historically in adults receiving DTG at approved/recommended paediatric and adult doses. Such data will be used to determine the final composition and weight band-based doses of the FDC product to be used in paediatric populations. More information on the efficacy, PK, safety and drug interaction potential of DTG based on an extensive program

of Phase I to III clinical trials can be found in the Investigator Brochure (IB) and supplement [GlaxoSmithKline Document Number RM2007/00683/11 and GlaxoSmithKline Document Number 2017N352880_00).

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of DTG may be found in the Investigator's Brochure [GlaxoSmithKline Document Number RM2007/00683/11] and Supplement to DTG Investigator's Brochure [GlaxoSmithKline Document Number 2017N352880_00]. The following section outlines the risk assessment and mitigation strategy for this protocol. Of note, the events noted in the table below were observed with the repeated doses of DTG at 50 mg. The risk of these events would be significantly lower for the single doses (2 x 5 mg dispersible tablets dispersed in water) being used in this protocol.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy[a]
	Investigational Product (IP) [DTG] **Refer to IB and IB Supplement for additional information**	
Hypersensitivity reaction (HSR) and rash	HSR has been observed uncommonly with DTG. Rash was commonly reported in DTG Phase IIb/III clinical trials; episodes were generally mild to moderate in intensity; no episodes of severe rash, such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and erythema multiforme were reported.	• *Participants with history of allergy/sensitivity to any of the study drugs are excluded (Section 5.2)* • *Specific/detailed toxicity management guidance is provided for HSR and rash (Section 11.6).* • *For Grade 3/4 rash, participants must permanently discontinue study drug and be withdrawn from the study (Section 7.1)* • *The participant informed consent form includes information on this risk and the actions participants should take in the event of an HSR or associated signs and symptoms.*
Neural tube defects	In one observational study in Botswana, preliminary results show that among women who were taking DTG when they became pregnant, approximately 0.9% had babies with neural tube defects compared to a background rate of 0.1%.	*Women of childbearing potential cannot participate in the study.*
Drug induced liver injury (DILI) and other clinically significant liver chemistry elevations	Non-clinical data suggested a possible, albeit low, risk for hepatobiliary toxicity with DTG. Drug-related hepatitis is considered an uncommon risk for antiretroviral therapy (ART) containing DTG regardless of dose or treatment population. A review of post-marketing data found that the number of cases reporting particularly severe liver dysfunction was found to be very low in the context of exposure to DTG and DTG/ABC/3TC. The reported cases of severe liver dysfunction (including acute hepatic failure) are complex with potential confounding factors but in a very small number of cases, drug-induced liver injury is likely and the role of DTG containing regimens cannot be ruled out particularly in those involving DTG with ABC/3TC or DTG/ABC/3TC.	*Participants meeting either of the following criteria during the screening period are excluded (Section 5.2).* • *Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).* • *Alanine Aminotransferase (ALT) or bilirubin >1.5x upper limit of normal (ULN).* *Specific/detailed liver stopping criteria and toxicity management guidance is provided for suspected DILI or other clinically significant liver chemistry elevations (Section 11.6, Appendix 6).*

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy[a]
	Investigational Product (IP) [DTG] Refer to IB and IB Supplement for additional information	
Renal function	Mild elevations of creatinine have been observed with DTG which are related to a likely benign effect on creatinine secretion with blockade of organic cation transporter 2 (OCT-2). DTG has been shown to have no significant effect on glomerular filtration rate (GFR) or effective renal plasma flow.	*Increases in serum creatinine due to DTG are not expected to have any adverse effect and will reverse during the wash out period after each single dosing of DTG, and; therefore, do not require mitigation for this protocol.*
Risks Associated with Study Procedures		
Cannulation	During cannulation more than one attempt may be needed to insert the cannula in a vein of a participant and it is possible that bruising and/or inflammation may be experienced at the site of cannulation.	• *A vein assessment will be conducted at screening to ensure only volunteers with veins suitable for multiple venepuncture and cannulation are enrolled.* • *Cannulation and/or venepuncture will only be performed by staff who are trained in these procedures*
ECG Collection	Electrocardiogram stickers on the participants' chests and limbs may cause some local irritation and may be uncomfortable to remove.	• *Participants will be monitored to ensure any local irritation does not persist.* • *Up to 2.5% hydrocortisone cream is permitted to relieve irritation from ECG leads.*

a. Careful monitoring of events will be conducted using serious adverse event (SAE) reports and alerts for Grade 3/4 laboratory toxicities (per Division of Acquired Immune Deficiency Syndrome [DAIDS] toxicity grading for HIV-infected patients). Serious/severe events will be managed appropriately including, but not limited to, withdrawal of investigational product (IP), and will be followed to resolution as per Sponsor's standard medical monitoring practices.

2.3.2. Benefit Assessment

This is a study in healthy participants and as such there is no expected benefit to administration of DTG. Participation in this study may contribute to the process of developing new therapies for HIV. There may be benefit to participants from the medical evaluations and assessments that could identify conditions that the participant was previously unaware.

2.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with DTG are justified by the anticipated benefits that may be afforded to paediatric patients with HIV. The events noted in Section 2.3.1 were observed with the repeated doses of DTG. The risk of these events would be significantly lower for the single doses being used in this protocol.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
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	
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, $t_{½}$, λz, $\%AUC_{ex}$, $AUC_{(0-24)}$, $AUC_{(0-72)}$, CL/F, Vz/F, Ct, and 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

4. STUDY DESIGN

4.1. Overall Design

This is an open-label, single-centre, single dose study in healthy adult participates 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. 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).

Participants will be admitted to the clinic the morning before dosing (i.e. Day -1) of each inpatient period. Each inpatient period will consist of 48 hours of post-dose assessments.

There will be one outpatient visit per Period for PK assessment at approximately 72 hours post dose. This will be followed by a washout of at least 7 (-4 hours) days between doses of study medication. The total length of study participation may be up to 8 weeks including screening, 3 dosing sessions, and follow-up. The follow-up visit will occur 7 to 14 days after the last dose of study drug. Participants will receive a single oral dose of study treatment during each inpatient period. At Follow-up, participants with no ongoing adverse events (AEs) or Vital Sign/Laboratory measures of clinical concern may be followed virtually by the site via telephone contact.

Note: The -4 hours is an allowed tolerance window to the 7-day washout and is to enable the study site and participants flexibility in scheduling admission and dosing for subsequent dosing periods (i.e., treatment periods 2 and/or 3).

4.2. Formulation Decision

Following the Dosing Periods, a preliminary data review will be conducted. The preliminary review will utilize data from Dosing Periods 1, 2, and 3 (i.e., single reference dose and 2 liquid prototype DTG formulations). For the preliminary formulation decision, data must be available from a minimum of 16 participants who have completed the planned safety and PK assessments up to 72 hours after dosing. An evaluable participant must also have received the relevant prototype and reference formulation(s) for the comparisons of interest (e.g., a prototype formulation(s) and the reference). If full data, as described below, are not available for 16 participants, the principal investigator (PI), scientific lead and Sponsor will take a decision as to whether the data available are sufficient to support the formulation selection decision. If data in fewer than 16 participants are used in the decision process, additional participants will not be dosed to increase the number of participants in the completed regimen.

The following data will be available to the Sponsor and the site:

- Plasma concentrations of DTG.
- Nominal time PK parameter estimates of DTG $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, $AUC_{(0-24)}$, t_{max}, C_{max} and $t_{1/2}$.

In evaluating a prototype formulation for success, the Sponsor and the site will consider the above listed data within the context of the geometric mean ratios (GMR) and 90% CIs for DTG (see Table 4 in Section 9.2.2). If the nominal time PK estimates for a prototype fall within the GMR and 90% CI limits defined in Section 9.2.2.

The decision on formulation selection will be made by the site's study team (i.e., PI, scientific lead and pharmacokineticist) and Sponsor study team (at a minimum the Sponsor's Medical Monitor, Clinical Pharmacokinetics Modelling and Simulation [CPMS] and Medicinal Product Development Lead). The decision will be documented and signed by the PI as per the site's current standard operating procedure. Evidence of the decision will be retained in the Investigator Site File and GSK Trial Master File.

See also Section 9.4.2.

4.3. Scientific Rationale for Study Design

Human Immunodeficiency Virus (HIV) is a retrovirus that infects primarily cluster of differentiation 4 (CD4) + T lymphocytes where it establishes latency. HIV-1 infection is associated with a progressive decrease in CD4+ T lymphocytes and an increase in viral load resulting in the destruction of the immune system and leading to the acquired immunodeficiency syndrome (AIDS) defined by the presence of one or more opportunistic infections. In the absence of treatment, HIV/AIDS is associated with serious morbidity and mortality. Combination antiretroviral therapy has demonstrated significant improvement in AIDS-related morbidity and mortality.

As the treatment of HIV in paediatric patients is a life-long endeavour, the development of new agents remains essential for overcoming drug resistance and toxicity, improving treatment compliance, and providing new options in cases where a lack of paediatric formulations or cross-resistance within a class limit the options available for children. A liquid formulation of DTG would provide a new option for new borns of up to approximately 6 weeks of age who have acquired or been born with HIV.

The purpose of the present study is to evaluate the relative bioavailability of experimental liquid formulations of DTG relative to administration of a 2 x 5 mg DTG dispersible tablets dispersed in water, in healthy adult participants.

4.4. Justification for Dose

The European Medicines Agency (EMEA)-approved adult dose of DTG for treatment-naive and non-INI resistant treatment-experienced HIV-infected patients is 50 mg once daily, alone or in combination with other antiretroviral drugs.

This relative bioavailability study intends to test 2 neonatal formulations with different strengths currently under development in a sequential design in healthy adult subjects. Paediatric dispersible tablet (5mg) will be used as reference. Selection of the reference dose (2 x 5 mg DTG dispersible tablets dispersed in water) will be based on the neonatal formulation strength to compare similar doses of the two formulations. Relative bioavailability of the previous 5 mg dispersible tablet (5x5mg) was studied in study 205893 against 25mg film coated tablet. This study will be used to bridge the neonatal formulation bioavailability with the 50mg film coated tablets currently being used in adults.

4.5. Discontinuation / Stopping Study

The study will be halted, and the risk to other participants evaluated, prior to a decision as to whether to terminate the study if any of the following criteria are met:

- The occurrence of an SAE considered at least possibly related to DTG administration in one participant.
- The occurrence of severe, non-serious AEs considered at least possibly related to DTG administration in 2 participants.

Relatedness will be determined by the investigator. If the study is halted, a temporary halt will be submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) and ethics committee (EC) in the form of a substantial amendment. The study will not be resumed until a further substantial amendment to resume the study is submitted and approved by MHRA and EC

4.6. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities.

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the Schedule of Activities for the last participant in the trial globally.

The EC and MHRA should be notified in writing of the conclusion of the study within 90 days of the end of the study, or within 15 days if the study is terminated early, clearly explaining the reasons for the termination.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

The site will have a full medical history from each participant's general practitioner within the last 12 months, prior to enrolment in the study. Participants will be recruited from the site panel or by direct advertising to the public.

Before participants are admitted to the clinic, The Over Volunteering Prevention System will be checked to ensure that each participant has not participated in a study at another site within at least 3 months of the dosing date.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be 18 to 55 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac evaluation.

Weight

3. Body weight ≥50 kg (110 lbs.) for men and ≥45 kg (99 lbs) for women and body mass index (BMI) within the range 18.5-31.0 kg/m^2 (inclusive).

Sex

4. Male and/or female

- Male Participates: No restrictions
- Female Participants: - A female participant is eligible to participate if she is not pregnant or breastfeeding, and is not a woman of childbearing potential (WOCBP; see Appendix 4, Section 11.4)

If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

- Additional requirements for pregnancy testing, if needed, during and after study intervention are located in Appendix 2.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

5. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. History or presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study intervention; or interfering with the interpretation of data.
2. Abnormal blood pressure as determined by the investigator.
3. Alanine transaminase (ALT) >1.5x upper limit of normal (ULN).
4. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
5. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
6. QT correction using Fridericia Formula (QTcF) >450 msec

NOTES:

- The QTc is the QT interval corrected for heart rate according to Fridericia's formula (QTcF), and/or another method, machine-read or manually over-read.
- The specific formula that will be used to determine eligibility and discontinuation for an individual participant (Fridericia's) is determined prior to initiation of the study. Several different formulae cannot be used to calculate the QTc for an individual participant and then the lowest QTc value used to include or discontinue the participant from the trial.

Prior/Concomitant Therapy

7. Past or intended use of over-the-counter or prescription medication (including herbal medications) within 7 days prior to dosing. Paracetamol, as listed in Section 6.5, is allowed.
8. History of allergy or sensitivity to DTG.

Prior/Concurrent Clinical Study Experience

9. Participation in the study would result in loss of blood or blood products in excess of 500 mL within 56 days.
10. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day.
11. Current enrollment or past participation within the last 30 days before signing of consent in this or any other clinical study involving an investigational study intervention or any other type of medical research.

Diagnostic assessments

12. Presence of Hepatitis B surface antigen (HBsAg), or a positive hepatitis B core antibody with a negative hepatitis B surface antibody at screening
13. Positive Hepatitis C antibody test result at screening.

    NOTE: Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained.

14. Positive Hepatitis C RNA test result at screening or within 3 months prior to first dose of study intervention

    NOTE: Test is optional and participants with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing.

15. Positive pre-study drug/alcohol screen.
16. Positive human immunodeficiency virus (HIV) antibody test.
17. Regular use of known drugs of abuse.

Other Exclusions

18. Regular alcohol consumption within one month prior to the study defined as:

    - For the United Kingdom an average weekly intake of >14 units for males or females. One unit is equivalent to 8 g of alcohol: a half-pint (~240 mL) of beer, 1 glass (125 mL) of wine or 1 (25 mL) measure of spirits.

19. Urinary cotinine levels indicative of smoking or history or regular use of tobacco- or nicotine-containing products (e.g. nicotine patches or vaporizing devices) within 6 months prior to screening.

To assess any potential impact on participant eligibility with regard to safety, the investigator must refer to the IB and supplements, approved product labels, and/or local prescribing information for detailed information regarding warnings, precautions, contraindications, AEs, drug interactions, and other significant data pertaining to the study drugs.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

- Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice [and/or pummelos, exotic citrus fruits, grapefruit hybrids or fruit juices] from 7 days prior to the first dose of study medication until after the final dose.
- Refrain from consumption of poppy seeds for 48 hours before screening, and from 48 hours before admission to each study period until after collection of the final PK sample in that period.
- Once in the clinical unit, participants will not be allowed to eat anything other than the food provided by the study centre.

5.3.1.1. Fasting Conditions

During the overnight period from Day -1 to Day 1 of each dosing period:

- An evening meal and/or snack will be provided by the unit (e.g. on Day -1).
- Participants must then fast from all food and drink (except water) for 10 hrs pre-dose and prior to any clinical laboratory evaluations (except repeat evaluations).
- Water is permitted with dosing (240 mL) for all Treatments and at all times except 1 hour pre-dose through 2-hours post-dose.
- No food is allowed for at least 4 hours post-dose.

5.3.1.2. Fed Conditions

With the exception of the period outlined in Section 5.3.1.1, participants will receive all other meals as defined as standard for the study centre.

5.3.2. Caffeine, Alcohol, and Tobacco

- During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 24 hours before the start of dosing until after collection of the final pharmacokinetic (PK) and/or sample.
- During each dosing session, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK and/or sample.

- Use of tobacco products will not be allowed from screening until after the final follow-up visit.

5.3.3. Activity

- Participants will abstain from strenuous exercise for 72 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (e.g., watching television, reading).

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants will be assigned a new participant number.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Table 3 Study Interventions

Study Treatment				
Arm Name	**Reference Treatment**	**Possible Prototype (Test) Liquid Formulations**		
		Ingredient:	**A**	**B**
Intervention name:	Dolutegravir (TIVICAY), 5 mg	Dolutegravir Sodium	0.526	0.211
		Ethylcellulose (Ethocel Standard 20 Premium)		
		Miglyol 812N (Excipient Grade – (Triglycerides, Medium Chain Ph Eur, USP-NF, JPE))	to 100.000	
		Glycerol (Ph Eur)		to 100.000
		Formula Description	Suspension	Solution/liquid
Type	Drug			
Dose Formulation components:	D-Mannitol, Microcrystalline Cellulose, Povidone, Sodium Starch Glycolate, Silicified Microcrystalline Cellulose, Crospovidone, Calcium Sulfate Dihydrate, Sucralose, Strawberry Cream Flavour, Sodium Stearyl Fumarate, White film coat (Contains: Hypromellose, Polyethylene Glycol and Titanium Dioxide)	Refer to IMPD for prototype No non-pharmacopoeial nor novel excipients will be used TBD (see above)		
Formulation Description	Dispersible tablets	Oral Suspension / Oral Liquid (see below)		
Unit dose strength(s)/Dosage level(s):	2 x 5 mg DTG dispersible tablets dispersed in water			
			5mg/mL Dolutegravir (as Dolutegravir Sodium), in miglyol 812N vehicle (oral suspension)	2mg/mL Dolutegravir (as Dolutegravir Sodium) (glycerol vehicle) (oral liquid)
Route of Administration	Oral			
IMP	Yes			
Sourcing	Provided centrally by Sponsor	Manufacture on site by Quotient Sciences		
Physical description:	White, round, film coated tablets debossed with 'SV H7S' on one side and '5' on the other side.	See above		
Method for individualizing dosage:	Oral via dosing cup	TBC (Oral via dosing syringe)		

6.2. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study intervention are provided in the Study Reference Manual.
- Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label, single-centre study.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrolment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

The Medical Monitor will be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Paracetamol at doses of ≤2 grams/day, is permitted for use any time during the study. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the Medical Monitor if required.

Hydrocortisone cream (2.5%) is permitted to relieve irritation from ECG leads.

6.6. Dose Modification

This is a single dose study in healthy participants, there are no planned dose modifications.

6.7. Intervention after the End of the Study

There will be no intervention available to participants following the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

If participants prematurely discontinue the study, additional replacement participants may be recruited at the discretion of the Sponsor in consultation with the investigator.

Replacement participants enrolled will be dosed with the next planned treatment of the withdrawn participant, and they will not receive any treatment that the withdrawn participants already received with the exception of the need to increase participant numbers to obtain the minimum number of evaluable participants required for the preliminary decision, and to obtain data in any other treatment that is required for a valid comparison. Replacement participants will receive the required treatments as planned for the original participant and the minimum washout period will be respected with regard to the timing of dosing.

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will not remain in the study to be evaluated for future pharmacokinetic measures. See the SOA for data to be collected at the time of discontinuation of study intervention.

Participants must be discontinued from the study for any of the following reasons:

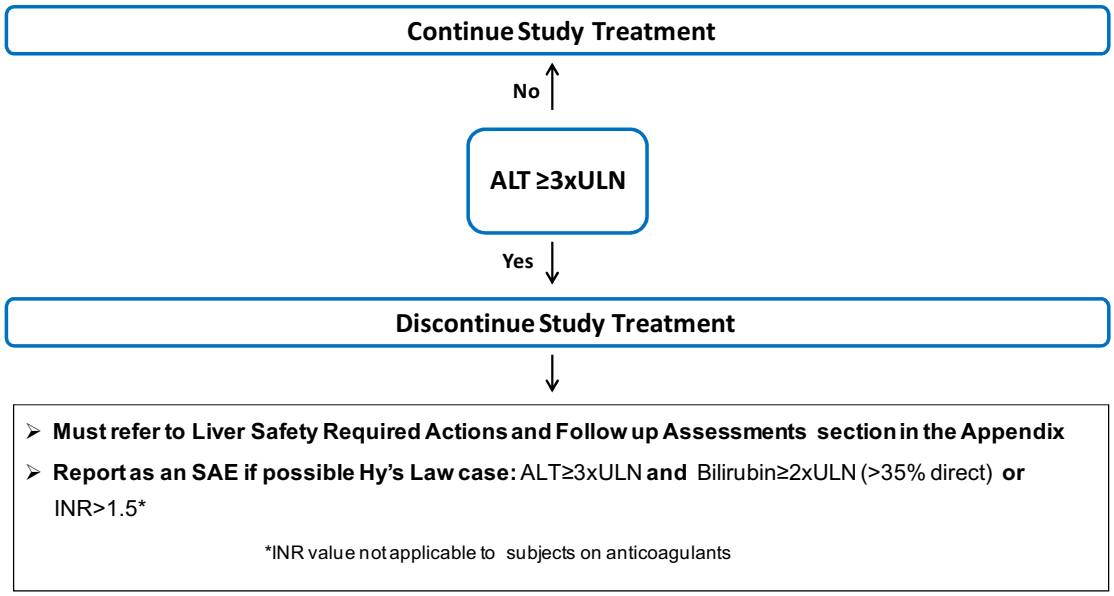
- Liver toxicity where stopping criteria specified in Section 7.1.1 are met and no compelling alternate cause is identified;
- Allergic reaction or Rash criteria as described in Appendix 6 Section 11.6 are met and no compelling alternate cause is identified.
- Renal toxicity as specified in Appendix 6 Section 11.6 are met and no compelling alternate cause is identified;
- Grade 4 clinical AE considered causally related to study drug;
- QTcF >500msec or change from baseline: QTc >60msec (Section 7.1.2).
- Pregnancy (intrauterine), regardless of termination status of pregnancy. (NOTE: Women of child bearing potential are not allowed to participate in this study).

7.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

Study intervention will be discontinued **for a participant** if liver chemistry stopping criteria are met:

Figure 2 Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Abbreviations: ALT = alanine transaminase; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal.

Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 7, Section 11.7.

Study intervention restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study is not allowed.

7.1.2. QTc Stopping Criteria

A participant that meets the bulleted criterion based on the average of triplicate ECG readings will be withdrawn from study intervention. There are no planned ECG collections post-dose in this study; however, additional ECGs may be performed during the study at the discretion of the investigator.

- QTcF > 500msec,
- Change from baseline: QTc >60msec.

NOTES:

- The *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.
- For example, if a participant is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual participant as well.
- Once the QT correction formula has been chosen for a participant's eligibility, the *same formula* must continue to be used for that participant *for all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.
- The QTc will be based on the average of triplicate ECG readings obtained over a brief (e.g., 5-10 minute) recording period.

See the SoA for data to be collected at the time of intervention discontinuation or follow-up for any further evaluations that need to be completed.

7.1.3. Temporary Discontinuation

This Section is not applicable to this study.

7.1.4. Study Termination

After the start of protocol activities but prior to the commencement of dosing, the study may be terminated by the Sponsor and investigator without consultation with the MHRA and EC. The end of the trial must be notified to the MHRA and EC immediately and at the latest within 15 days after the study is terminated, clearly explaining the reasons. A description of follow up measures taken for safety reasons if applicable, will also be provided.

If the study is abandoned prior to commencement of any protocol activities, the principal investigator (PI) or Sponsor must notify the end of trial to the EC and MHRA by letter outlining the reasons for abandonment of the trial.

Once exposure to DTG has begun, the study will be completed as planned unless the following criteria are satisfied that require a temporary halt or early termination of the study.

- The occurrence of serious or severe AE(s), as defined in Appendix 4 (Section 11.4), if considered to be related to study treatment.

- New information regarding the safety of the study treatment that indicates a change in the risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for participants in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises participant safety.

If any of the above occurs, the study will be terminated if careful review of the overall risk/benefit analysis described in Section 2.3 demonstrates that the assumptions have changed and that the overall balance is no longer acceptable. In these circumstances termination can only take place with the agreement of the investigator and Sponsor. The MHRA and EC will be informed of study termination.

If it becomes necessary to consider termination of the study after dosing has begun, dosing may be suspended pending discussion between the investigator and Sponsor.

Dosing will be stopped immediately on safety grounds.

The study may be terminated or suspended at the request of the MHRA or EC.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation or follow-up for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Protocol waivers or exemptions are not allowed
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- A participant will be allowed to leave the premises following completion of study-specific procedures at 48 hours post-dose providing that:
    - No AEs have been reported during the study visit
    - The participant responds positively when asked "How are you feeling?"

- If any of these conditions are not met, then the participant may only be allowed to leave the clinical unit with the authorisation of the investigator or appropriately qualified delegate.

8.1. Efficacy Assessments

This Section is not applicable to this study.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height (screening only) and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- Temperature (collected as standard for the site), pulse rate, and systolic and diastolic blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in a supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure \ vital signs measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones) and will be measured in a supine position and will include temperature, systolic and diastolic blood pressure, and pulse.
- The acceptable deviations from the nominal vital signs measurement time points are:
  - Discharge vital signs measurements will be taken ±1 hour from the nominal time point.
- If a participant shows an abnormal assessment at any stage, repeat measurements may be made and the abnormality followed to resolution if required. Additional measurements may be taken as deemed necessary by the investigator.
- Any clinically significant abnormality, including changes from baseline (pre-dose Day 1), must be reported as an AE.

8.2.3. Electrocardiograms

- 12-lead ECGs will be performed with the participant in a supine position having rested in this position for at least 10 minutes beforehand.
- Single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 7 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- The acceptable deviations from the nominal ECG measurement time points are:
  - Discharge ECG measurements will be taken ±1 hour from the nominal time point.
- If a participant shows an abnormal assessment at any stage, repeat measurements may be made and the abnormality followed to resolution if required. Additional measurements may be taken as deemed necessary by the investigator.
- Any clinically significant abnormality, including changes from baseline (pre-dose Day 1), will be reported as an AE.

8.2.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- Blood samples for scheduled laboratory assessments will be taken following an overnight fast.
- The acceptable deviations from the nominal blood sampling time points for laboratory assessments are:
  - The pre-dose blood sample will be taken ≤2 hours before dosing
- The acceptable deviations from the nominal urine sampling time points for urinalysis are:
  - The pre-dose urine sample will be taken ≤3 hours before dosing or the first void of the day
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the case report form (CRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 7 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period-of-time judged reasonable by the investigator, the aetiology should be identified and the sponsor notified.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study (see Section 7).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the start of intervention until the follow-up visit at the time points specified in the SoA (Section 1.3). However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a ViiV product will be recorded from the time a participant gives consent to participate in the study.
- All AEs will be collected from the start of intervention until [the follow-up visit] at the time points specified in the SoA (Section 1.3).
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.
- Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g., summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

Women of child bearing potential are not permitted to participate in this study.

8.4. Treatment of Overdose

For this study, any dose of dolutegravir greater than 50 mg within a 24-hour period ±4 hours will be considered an overdose.

ViiV Healthcare does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until dolutegravir can no longer be detected systemically (at least 7 days).
3. Obtain a plasma sample for PK analysis within 3 days from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).

4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

8.5.1. Blood Sample Collection

Blood samples for pharmacokinetic (PK) analysis of DTG will be collected at the time points indicated in the SoA via venepuncture and/or cannulation, Section 1.3. The 4-hour post-dose sample must be drawn prior to the participants' first post-dose meal. Instructions for the collection and handling of biological samples are provided below. The actual date and time of each blood sample collection will be recorded.

For each time point identified in the SoA, Section 1.3 , 2 mL of blood will be collected into di-potassium ethylenediaminetetraacetic acid (K_2EDTA) tubes. Details of PK blood sample collection, processing, storage and shipping procedures are provided in the site provided SRM.

The acceptable deviations from the nominal post-dose blood sampling times are as follows:

- The pre-dose blood sample will be taken ≤1hour before dosing.
- Post-dose samples from >0 to 4 hours post-dose will be taken within ±2 minutes of the nominal post-dose sampling time.
- Post-dose samples from >4 to 12 hours post-dose will be taken within ±5 minutes of the nominal post-dose sampling time.
- Post-dose samples from >12 to 48 hours will be taken within ±15 minutes of the nominal post-dose sampling time.
- Post-dose samples for 72 hours will be taken within ±2 hours of the nominal post-dose sampling time.

8.5.2. Sample Processing Procedures

If a cannula is used, the cannula will be inserted into an arm vein within sufficient time prior to dosing, will be kept patent with normal saline, and will be removed after the last blood sample is collected or earlier if the participant requests. To avoid artificial dilution of the PK samples by saline, 0.5 mL of whole blood will be collected and discarded before each whole blood sample is collected.

Collect each serial whole blood PK sample as close as possible to the planned time relative to dosing detailed in the protocol. Collect a whole blood (2 mL) sample into a properly labelled K_2EDTA evacuated blood collection tube. Record the date and exact time that each sample is collected in the CRF.

Samples will be used to evaluate the PK of dolutegravir. Each sample will be divided into 2 aliquots. Samples collected for analyses of dolutegravir whole blood concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

8.5.3. Sample Storage Conditions

Immediately after collection, gently invert (DO NOT SHAKE) the blood collection tube 8-10 times to mix the K_2EDTA anti-coagulants with the whole blood and place the samples at room temperature. Within 45 minutes of sample collection, centrifuge for 10 minutes, at 1500 - 2000 G, in 4°C. Within 30 minutes of centrifugation, using a polyethylene pipette, transfer plasma into separate, single, and appropriately labelled 2 mL Amber Sarstedt tubes. Immediately freeze the storage tubes in an upright position at -20°C.

8.5.4. Sample Analysis

DTG will be extracted from plasma using protein precipitation followed by ultra-performance liquid chromatography triple quadrupole mass spectrometry (UPLC-MS/MS) using the previously validated method, Quantitation of GSK1349572 in Human Plasma via UPLC with MS/MS Detection (PPD method number, P1170.02; GlaxoSmithKline Document Number 2012N147635_00). The analysis will be performed by PPD, 3230 Deming Way, Middleton, WI, USA. The DTG sample analysis will be under the management of Bioanalysis, Immunogenicity and Biomarkers (BIB), PTS, GlaxoSmithKline. Raw data will be archived at the bioanalytical site.

Genetic analyses will not be performed on these whole blood samples. Participant confidentiality will be maintained.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

This study is designed to estimate the relative bioavailability of 2 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 the 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.

9.2. Sample Size Determination

9.2.1. Sample Size Assumptions

A maximum of 18 participants will be enrolled to receive study intervention such that approximately 16 evaluable participants complete the study. Precision estimates for both the mean treatment ratios and variability for the primary objectives of the study based on 16 participants completing the study have been calculated.

The within subject coefficient of variation (CVw%) for the PK parameters in the GSK study 205893 following 5-mg dispersible DTG tablet was not available in the Clinical Pharmacology Study Report; therefore, the within subject coefficient of variation for the PK parameters was calculated using mixed model with treatment and period as fixed effects and subject as random effect on $\log_e$-transformed parameters. The estimates of within subject coefficient of variation (CVw %) are 16.7% for $AUC_{(0-\infty)}$ and $AUC_{(0-t)}$ and 20.8% for C_{max}. A CVw% of 20.8% is a conservative estimate on which the sample size calculation was based.

For a sample size of 16 evaluable participants, it is estimated that for a point estimate of the ratio of geometric means (prototype: reference) of 1.00 the 90% CI would be approximately (0.88, 1.14) for the $AUC_{(0-\infty)}$, $AUC_{(0-t)}$, and C_{max} parameters.

9.2.2. Sample Size Sensitivity

Using estimates of parameter (any PK parameter, e.g., AUC, C_{max}) variability [16.7%, 23.5% and 27.5%] and point estimate of geometric mean ratio of 0.90, 0.95, 1.00, 1.05, 1.10, and 1.15, the 90% CI for 16 evaluable participants has been calculated (Table 4).

Table 4 Precision Estimate of the Mean for DTG

Within Subject variability CVw (%)	Geometric Mean Ratio	(90% Confidence Interval)
16.7	0.90	(0.81, 1.00)
	0.95	(0.86, 1.05)
	1.00	(0.90, 1.11)
	1.05	(0.95, 1.16)
	1.10	(0.99, 1.22)
	1.15	(1.04, 1.27)
23.5	0.90	(0.78, 1.04)
	0.95	(0.82, 1.10)
	1.00	(0.87, 1.15)
	1.05	(0.91, 1.21)
	1.10	(0.95, 1.27)
	1.15	(1.00, 1.33)
27.5	0.90	(0.76, 1.06)
	0.95	(0.80, 1.12)
	1.00	(0.85, 1.18)
	1.05	(0.89. 1.24)
	1.10	(0.93, 1.30)
	1.15	(0.97, 1.36)

For example, based upon the estimate of variability (CVw%) of 27.5% for DTG and a point estimate of the ratio of geometric means of 1.05; it is estimated that the 90% CI for the means of the PK parameter (e.g., AUCs, C_{max}) will be (0.89, 1.24).

9.3. Populations for Analyses

An evaluable participant will have completed the planned safety and PK assessments up to 72 hours after dosing. An evaluable participant must also have received the relevant prototype and reference formulations for the comparisons of interest (e.g. a prototype formulation and the reference).

For purposes of analysis, the following populations are defined:

Population	Description
Screened	All participants who sign the ICF
All Participants	All participants who receive at least one dose of study medication. This population will be used for the study population and safety displays.
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.

9.4. Statistical Analyses

Final analyses will be performed after the completion of the study and final dataset authorization.

Data will be listed and summarized according to GlaxoSmithKline reporting standards where applicable. Listings will be sorted by participant, period, day, and time, noting treatment. Summaries will be presented by treatment, day and time.

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.

Baseline or pre-dose assessment is the last available assessment prior to time of the first dose unless it is specified otherwise. If there are multiple assessments collected on the same scheduled time, the average of these assessments will be used. For tabulated safety summaries, only the scheduled assessments will be included in the summary tables.

Version 9.3 or higher of the Statistical Analysis Software (SAS) system will be used to analyze data as well as to generate tables, listings, and figures.

Complete details will be documented in the Reporting and Analysis Plan (RAP).

9.4.1. Primary and Secondary Analyses

Comparisons will be made for the single dose PK parameters of DTG, as described in Table 5. For preliminary formulation decision see Section 4.2.

Table 5 Primary and Secondary Comparisons of Interest

DTG PK Parameter	Prototype	Reference	Assessment
$AUC_{(0-\infty)}$, $AUC_{(0-t)}$, C_{max}, CL/F, $AUC_{(0-24)}$, C_{24}, $t_{1/2}$	Prototype Treatments A and B	Reference Treatment	Relative bioavailability

9.4.2. Pharmacokinetic Analyses

Pharmacokinetic analyses will be the responsibility of the Clinical Pharmacology Modelling & Simulation department within GSK or their designee. Plasma DTG concentration-time data will be analyzed by non-compartmental methods with Phoenix WinNonlin. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following pharmacokinetic parameters will be determined, as data permit: C_{max}, t_{max}, $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, $AUC_{(0-24)}$, $AUC_{(0-72)}$, $t_{1/2}$, t_{lag}, C_{24}, CL/F, t_{max}, t, λz, %AUCex, Vz/F and Ct.

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

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

The PK parameters for DTG (except t_{max} and t_{lag}) will be $\log_e$-transformed and separately analysed using a mixed effects model with fixed effect terms for treatment for each treatment comparison specified in Section 9.4.1. Participant will be 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 prototype 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 prototype and reference treatments.

The t_{max} will be analysed using the non-parametric Wilcoxon matched pair method to calculate point estimates and associated 90% confidence intervals for the median differences between test and reference treatments.
Further details will be provided in the RAP.

9.4.3. Safety Analyses

Safety data will be presented in tabular format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards. No formal statistical analysis of the safety data will be conducted.

The details of the statistical analyses of safety and PK data will be provided in the Reporting and Analysis Plan.

All safety analyses will be performed on the All Participants Population.

9.5. Preliminary Analyses

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 (see Section 4.2). .
Treatment and period information may be used in the analyses.

10. REFERENCES

GlaxoSmithKline Document Number 2012N147635_00. Quantitation of GSK1349572 in Human Plasma via UPLC with MS/MS Detection. 14-August-2012.

GlaxoSmithKline Document Number 2017N352880_00: Supplement to DTG Investigator's Brochure. 11-December-2017.

GlaxoSmithKline Document Number RM2007/00683/11: GSK1349572 Clinical Investigator's Brochure. 13-October-2017.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

11.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- The study must be approved by the Competent Authority (CA) prior to initiation.
- Any substantial amendments to the protocol will require IEC/IRB and CA approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

11.1.2. Protocol Amendments

After the protocol has been submitted to the MHRA and/or EC, any amendment must be agreed by the investigator after discussion with the sponsor and will be formally documented.

All substantial amendments will be submitted to the MHRA and/or EC for an opinion as required by current regulations.

If the participant information sheet (PIS) and ICF are updated as a result of an amendment, the new versions will be used to re-consent currently enrolled participants and must be provided to additional participants prior to their entry into the study.

11.1.3. Protocol Deviations

The study must be conducted in accordance with the Clinical Protocol. Should a protocol deviation occur, it must be promptly assessed in order to decide whether any of these non-compliances will be reported to the MHRA as a serious breach of GCP and the Clinical Protocol.

Protocol waivers are not acceptable.

Deviations from the protocol will be recorded in the source workbook as noted by the clinical staff. If necessary, the Sponsor will be informed of the deviation.

Any protocol deviations assessed as major will be discussed with the Sponsor in order to determine if the withdrawal criteria stated in Section 8 have been met.

11.1.4. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

11.1.5. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

11.1.6. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

11.1.7. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multi-centre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

11.1.8. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK/ViiV Healthcare will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- GSK intends to make anonymized patient-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided

by trial participants are used to maximum effect in the creation of knowledge and understanding

11.1.9. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

11.1.10. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Monitoring Plan.

11.1.11. Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

11.1.12. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multi-centre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

11.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 6 will be performed by The Doctors Laboratory, except for routine urinalysis, urine pregnancy test, urine drug screen and cotinine tests, and alcohol breath tests. These tests will be performed on-site according to site SOPs.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy Testing
  - Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria.
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted at the standard procedure for the site during the study and according to the Schedule of Assessments.
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy during the participant's participation in the study.

Table 6 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count Red Blood Cell (RBC) Count Hemoglobin Hematocrit	RBC Indices: Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	BUN	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT) / Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (fasted)	Calcium	Alkaline phosphatase	Creatine Kinase
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests (all tests to be conducted as standard for the study site)	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)] • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) • Hepatitis C RNA (when participant has a history of treated hepatitis C) • Creatinine clearance (or estimation of GFR using CKD-EPI$_{creatinine}$)			

NOTES :

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Appendix 7 All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

11.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

11.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of

Events NOT Meeting the AE Definition
the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

11.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
• Results in death
• Is life-threatening: The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect
Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

11.3.3. Recording and Follow-Up of AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the CRF. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
Every AE and SAE reported during the trial should be evaluated by the investigator and graded in the eCRF according to the DAIDS toxicity scales (see Appendix 5, Section 11.5 for a link to DAIDS toxicity). **Note:** Grade 4 DAIDS toxicity grades for laboratory parameters that are asymptomatic would not necessarily be considered SAEs, a clinical correlation would be necessary. Where a DAIDS toxicity scale is not available for a particular event or parameter, then the investigator will instead make an assessment of intensity using one of the following categories: • Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.

- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

Note: An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.

- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

11.3.4. Reporting of SAE to ViiV Healthcare/GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor by telephone.
- Contacts for SAE reporting are:

  Primary Medical Monitor
  PPD; FCP, MSc
  Director, Clinical Development Research and Development, ViiV Healthcare
  980 Great West Road
  Brentford, Middlesex, TW 9GS United Kingdom
  PPD
  PPD

  Back-up Medical Monitor
  PPD, M.D.
  Director, Clinical Development Research and Development, ViiV Healthcare
  Five Moore Drive, P.O. 13398
  Research Triangle Park, NC 27709-3398, USA
  PPD
  PPD

  All SAEs to SAE emails (use *both* addresses below):
  - PPD
  - PPD

11.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

11.4.1. Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
- A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT).
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

11.4.2. Collection of Pregnancy Information:

Women of child bearing potential are not allowed to participate in this study.

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study intervention by the investigator, will be reported to GSK as described in Appendix 3. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating will discontinue study intervention or be withdrawn from the study

11.5. Appendix 5: Division of AIDS Table For Grading The Severity Of Adult And Paediatric Averse Events Version 2.1, March 2017

VERSION 2.1, March 2017

The Division of AIDS Table for Grading the Severity of Adult and Paediatric Adverse Events ("DAIDS AE Grading Table") is a descriptive terminology which can be utilised for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Estimating Severity Grade for Parameters Not Identified in the Grading Table
The table in the link below should be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, all deaths related to an AE are to be classified as Grade 5.

Reference

U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Paediatric Adverse Events, Version 2.1. [March 2017].

Available at: https://rsc.tech-res.com/docs/default-source/safety/daids-ae-grading-table-mar2017.pdf MAR-2017).

11.6. Appendix 6: Toxicity Management

11.6.1. ANEMIA

Grade 1 (mild) haemoglobin decrease:

Any haemoglobin decrease meeting the definition of Grade 1 must be repeated with the following additional tests:

1. peripheral blood smear
2. indirect bilirubin (abnormal if increased >50% from baseline)
3. haptoglobin (abnormal if ≤ 25 mg/dL)
4. reticulocyte count (abnormal if ≥ 4%)

If the additional tests are within the normal range, participants may continue study medication. If one or more of the additional tests is abnormal or suggestive of haemolytic anaemia as specified above, participants will permanently discontinue study medication and be withdrawn from the trial. Participants should be followed up until resolution of anaemia.

Grade 2 (moderate) haemoglobin decrease:

Any haemoglobin decrease meeting the definition of Grade 2 must be repeated with the following additional tests:

1. peripheral blood smear
2. indirect bilirubin (abnormal if increased >50% from baseline)
3. haptoglobin (abnormal if ≤25 mg/dL)
4. reticulocyte count (abnormal if ≥4%)

If the additional tests are within the normal range, participants may continue study medication. If one or more of the additional tests is abnormal or suggestive of haemolytic anaemia as specified above, participants will permanently discontinue study medication and be withdrawn from the trial. Consultation with a Haematologist should be considered. Participants should be followed up until resolution of anaemia.

Grade 3 (severe) or Grade 4 (potentially life threatening) hemoglobin decrease:

Any hemoglobin decrease meeting the definition of Grade 3 or 4 must be repeated with the following additional tests:

1. peripheral blood smear
2. indirect bilirubin
3. haptoglobin
4. reticulocyte count

Participants will permanently discontinue study medication and be withdrawn from the trial. Consultation with a Haematologist should be considered. Participants should be followed up until resolution of anaemia.

11.6.2. TOTAL BILIRUBIN ELEVATION

Grade 1 (mild) bilirubin elevation (1.1 - 1.5 times ULN) or Grade 2 (moderate - 1.6-2.5 times ULN):

Any bilirubin value above the upper limit of normal must be repeated and fractionated (direct and indirect bilirubin). Subjects may continue study medication. Subjects should be followed up until resolution (return to baseline) of elevation.

Grade 3 (severe – 2.6-5.0 times ULN) or 4 (life-threatening - > 5.0 times ULN) bilirubin elevation:

Any bilirubin value above the ULN must be repeated and fractionated (direct and indirect bilirubin). Subjects will permanently discontinue study medication and be withdrawn from the trial. Subjects should be followed up until resolution (return to baseline) of bilirubin elevation.

11.6.3. AST AND ALT ELEVATION

See Appendix 7 [Section 11.7].

11.6.4. RASH

Grade 1 rash (Localized macular rash):

Participants with Grade 1 rash should be evaluated by the Investigator immediately. A dermatologist may be consulted and a biopsy may be obtained if recommended by the dermatologist. The study drug should be permanently discontinued if the following signs or symptoms are noted at any time:

1. Temperature >38.5°C
2. Lymphadenopathy
3. Pharyngitis
4. Any indication of internal organ involvement (hepatitis, nephritis)

In the absence of the above signs or symptoms, participants with Grade 1 rash may continue the study drug at the discretion of the Investigator. The participant should be advised to contact the Investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms worsen, or if mucosal ulceration develops. If the rash is considered to be most likely due to concomitant illness or non-study medication, standard management, including discontinuation of the likely causative agent, should be undertaken. If no other causative factor is found after clinical evaluation, the participant may be treated symptomatically until the rash resolves. Antihistamines, topical corticosteroids or antipruritic agents may be prescribed.

Grade 2 rash (Diffuse macular, maculopapular, or morbilliform rash OR Target lesions):

Participants with Grade 2 rash should be evaluated by the Investigator immediately. Digital photographs should be obtained. A dermatologist may be consulted and a biopsy

may be obtained if recommended by the dermatologist. The study drug should be permanently discontinued if the following signs or symptoms are noted at any time:

1. Temperature >38.5°C
2. Lymphadenopathy
3. Pharyngitis
4. Any indication of internal organ involvement (hepatitis, nephritis)

In the absence of the above signs or symptoms, participants with Grade 2 rash may continue the study drug at the discretion of the Investigator. It should be noted that oral mucosal **erosions** may be part of a Grade 2 rash. Any mucosal **ulceration** increases the severity of the rash to at least Grade 3. The participant should be advised to contact the Investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms worsen, or if mucosal ulceration develops. If the rash is considered to be most likely due to concomitant illness or non-study medication, standard management, including discontinuation of the likely causative agent, should be undertaken. If no other causative factor is found after clinical evaluation, the participant may be treated symptomatically until the rash resolves. Antihistamines, topical corticosteroids or antipruritic agents may be prescribed. The participant should remain on the study to be followed for safety and PK as outlined in Section 11.3 (Appendix 3).

Grade 3 rash (Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site):

Participants with a Grade 3 rash will permanently discontinue the study medication. The participant should be evaluated in the physician's office immediately and should be seen in the physician's office or contacted by phone every 2 days until the rash resolves. A dermatologist should be consulted and digital photographs and a biopsy should be obtained. Antihistamines, topical corticosteroids or antipruritic agents may be prescribed at the discretion of the Investigator. The participant should be advised to contact the Investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms appear, or if mucosal involvement develops. The participant should remain on the study to be followed for safety and PK as outlined in Section 11.3 (Appendix 3).

Grade 4 rash (Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)):

Participants with a Grade 4 rash will permanently discontinue the study medication. A dermatologist should be consulted and digital photographs and a biopsy should be obtained. Sponsor and GSK Medical Monitor should be notified of this serious adverse event within 24hr via phone or fax. The participant should be closely followed everyday until resolution of the reaction. The participant should remain on the study to be followed for safety and PK as outlined in Section 11.3 (Appendix 3).

11.6.5. ALLERGIC REACTION

Grade 1 allergic reaction (Pruitis without rash):

Participants with Grade 1 allergic reaction should be evaluated by the Investigator immediately. The study drug should be permanently discontinued if the following signs or symptoms are noted at any time:

1. Temperature > 38.5°C
2. Eosinophilia
3. Respiratory involvement including bronchospasm, laryngospasm, or angioedema
4. Any indication of internal organ involvement (hepatitis, nephritis)

In the absence of the above signs or symptoms, participants with Grade 1 allergic reaction may continue the study drug at the discretion of the Investigator. The participant should be advised to contact the Investigator immediately if there is any worsening of the allergic reaction and/or if any systemic signs or symptoms worsen. If the allergic reaction is considered to be most likely due to concomitant illness or non-study medication, standard management, including discontinuation of the likely causative agent, should be undertaken. If no other causative factor is found after clinical evaluation, the participant may be treated symptomatically until the rash resolves. Antihistamines, topical corticosteroids or antipruritic agents may be prescribed. The participant should remain on the study to be followed for safety and PK as outlined in Section 11.3 (Appendix 3).

Grade 2 allergic reaction (Localized urticaria):

Participants with Grade 2 allergic reaction should be evaluated by the Investigator immediately. The study drug should be permanently discontinued if the following signs or symptoms are noted at any time:

1. Temperature > 38.5°C
2. Eosinophilia
3. Respiratory involvement including bronchospasm, laryngospasm, or angioedema
4. Any indication of internal organ involvement (hepatitis, nephritis)

In the absence of the above signs or symptoms, participants with Grade 2 allergic reaction may continue the study drug at the discretion of the Investigator. The participant should be advised to contact the Investigator immediately if there is any worsening of the allergic reaction and/or if any systemic signs or symptoms worsen. If the allergic reaction is considered to be most likely due to concomitant illness or non-study medication, standard management, including discontinuation of the likely causative agent, should be undertaken. If no other causative factor is found after clinical evaluation, the participant may be treated symptomatically until the rash resolves. Antihistamines, topical corticosteroids or antipruritic agents may be prescribed. The participant should remain on the study to be followed for safety and PK as outlined in Section 7.1.1 and Appendix 7, Section 11.7.

Grade 3 allergic reaction (Generalized urticaria or angioedema):

Participants will permanently discontinue the study medication and be withdrawn from the trial. Participants will be treated as clinically appropriate. Participants should be

followed up until resolution of the adverse event and standard management should be undertaken.

Grade 4 allergic reaction (Anaphylaxis):

Participants will permanently discontinue the study medication and be withdrawn from the trial. Participants will be treated as clinically appropriate. Participants should be followed up until resolution of the adverse event and standard management should be undertaken.

Revised ACTG Toxicity Grade	Definitions	Investigator Action
Grade 1	Pruritus without rash	May continue therapy
Grade 2	Localized urticaria	May continue therapy
Grade 3	Generalized urticaria Angioedema	Discontinue Therapy
Grade 4	Anaphylaxis	Discontinue Therapy

11.6.6. Decline in Renal Function

Participants who experience an increase in serum creatinine from baseline of 45 micromoles/liter (micromol/L) (or 0.5 milligrams/deciliter [mg/dL]) or greater should have a confirmatory assessment. A urinalysis, urine albumin/creatinine and urine total protein/albumin ratios, serum cystatin C and an estimated GFR using the CKD-EPI (cystatin C) [Inker, 2012] should also be done at this confirmatory visit. If the creatinine increase is confirmed, the investigator should contact the study medical monitor to discuss additional follow-up and medical management.

References

Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T *et. al*. Estimating Glomerular Filtration Rate from Serum Creatinine and Cystatin C. *N Engl J Med* 2012; 367(1):20-9.

11.7. Appendix 7: Liver Safety: Required Actions and Follow-up Assessments

Table 7 Phase I liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	• ALT≥3xULN • If ALT≥3xULN **AND bilirubin**[1,2] ≥ 2xULN (>35% direct bilirubin) or **INR** >1.5, Report as an SAE. • See additional Actions and Follow Up Assessments listed below

Required Actions and Follow up Assessments	
Actions	**Follow Up Assessments**
• Report the event to GSK/ViiV **within 24 hours** • Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see **MONITORING** below) **MONITORING:** **If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5** • Repeat liver chemistries (include ALT, aspartate transaminase [AST], alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within **24 hrs** • Monitor participants twice weekly until liver chemistries resolve, stabilise or return to within baseline • A specialist or hepatology consultation is recommended **If ALT≥3xULN AND bilirubin < 2xULN and INR ≤1.5:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	• Viral hepatitis serology[3] • Obtain international normalized ratio (INR) and recheck with each liver chemistry assessment until the transaminases values show downward trend • Obtain blood sample for pharmacokinetic (PK) analysis, 72 hours of last dose[4] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form **If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that participant if ALT ≥3xULN and bilirubin ≥2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN and INR>1.5, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); the threshold value stated will not apply to participants receiving anticoagulants
3. Includes: Hepatitis A immunoglobulin (gM) antibody; HBsAg and HBcAb; Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing) and Hepatitis E IgM antibody

11.8. Appendix 8: Safety Reporting to Ethics Committee and Regulatory Authorities

Events Requiring Expedited Reporting

SUSARs are subject to expedited reporting to the MHRA, EMA and EC. In addition to SUSARs, other safety issues may qualify for expedited reporting where they might materially alter the current benefit-risk assessment of a study treatment or that would be sufficient to consider changes in the study treatments administration or in the overall conduct of the study, for instance:

- An increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important
- SAEs that occur after the participant has completed the clinical study where the sponsor considers them to be a SUSAR
- New events related to the conduct of the study or the development of the study treatments and likely to affect the safety of the participants, such as:
    - An SAE which could be associated with the study procedures and which could modify the conduct of the study
    - A major safety finding from a newly completed animal study (such as carcinogenicity)
    - Any anticipated end or temporary halt of a study for safety reasons and conducted with the same study treatments in another country by the same sponsor

Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

It is the responsibility of the Sponsor to determine whether a reported SAE fits the classification of a SUSAR and to notify the investigator of their decision as soon as possible.

Expedited Reporting of Events

It is the responsibility of the Sponsor to determine whether an event requires expedited reporting and to notify the investigator of their decision as soon as possible.

Where expedited reporting is required, the following procedures will be followed.

Fatal or life-threatening SUSARs:

- It is the responsibility of the sponsor to report fatal or life-threatening SUSARs to the MHRA and EMA as soon as possible, but no later than 7 calendar days after they first became aware of the reaction. This responsibility will be delegated to the pharmacovigilance provider (GSK/ViiV).
- The investigator is required to notify the EC of any SUSAR as soon as possible, but no later than 7 calendar days after they first became aware of the reaction.
- Any additional relevant information will be sent within 8 days of the report.

Other SUSARs:

- It is the responsibility of the Sponsor to report other SUSARs to the MHRA and EMA as soon as possible, but no later than 15 calendar days after they first became

aware of the reaction. This responsibility will be delegated to the pharmacovigilance provider (GSK/ViiV).
- The investigator is required to notify the EC of other SUSARs as soon as possible, but no later than 15 calendar days after they first became aware of the reaction.

Urgent Safety Measures

If Quotient Sciences or any of its staff or contractors becomes aware of an actual or potential urgent safety issue, then the sponsor must be immediately contacted so that appropriate urgent safety measures can be agreed. An urgent safety issue is defined as:
- An immediate hazard to the health or safety of participants enrolled in a clinical study
- A serious risk to human health or potentially a serious risk to human health.

An urgent safety issue may include issues with an investigational drug or comparators, study procedures, inter-current illness (including pandemic infections), concomitant medications, concurrent medical conditions or any other issues related to the safe conduct of the study or that pose a risk to study participants.

In exceptional circumstances of imminent hazard and to safeguard the health or safety of individuals, Quotient Sciences may take urgent safety measures before informing the sponsor, but the sponsor must be informed immediately after the hazard has resolved.

Quotient Sciences will take responsibility for informing appropriate competent authorities, and the EC.

Reporting of Urgent Safety Issues

Quotient Sciences is required to inform the appropriate competent authorities and the EC within 3 calendar days of the urgent safety issue.

Serious Breaches

It is the responsibility of the Sponsor to notify the licensing authority of any serious breach, which is likely to affect, to a significant degree, the safety or mental integrity of the participants of the study or the scientific value of the study.

All serious breaches will be notified to the MHRA within 7 days. The reporting will be performed by the party who suspects the serious breach.

11.9. Appendix 9: Abbreviations and Trademarks

Abbreviations

ABC	Abacavir
AE	Adverse Event
AIDS	Acquired immune deficiency syndrome
ALT	Alanine aminotransferase (SGPT)
ART	Antiretroviral Therapy
ARV	Antiretroviral
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the concentration-time curve
$AUC_{(0-t)}$	Area under the plasma concentration-time curve from time of dose to last measurable concentration
$AUC_{(0-\infty)}$	Area under the plasma concentration-time curve from time of dose extrapolated to infinity
$AUC_{(0-24)}$	Area under the plasma concentration-time curve from time of dose to 24 hr
$AUC_{(0-72)}$	Area under the plasma concentration-time curve from time of dose to 72 hr
%AUCex	% of $AUC_{(0-\infty)}$ that was extrapolated
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
C24	Concentration at 24 hours after dose administration
CA	Competent Authority
CI	Confidence Interval
CL/F	Apparent oral clearance
C_{max}	Maximum observed concentration
C_{24}	Observed concentration at 24h post-dose
CD4	Cluster of differentiation 4
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CRF	Case Report Form
Ct	Last quantifiable concentration
CV	Coefficient of variance
CVb	Between subject coefficient of variation
DAIDS	Division of Acquired Immunodeficiency Syndrome
DILI	Drug-Induced Liver Injury
DNA	Deoxyribonucleic acid
DT	Dispersible tablet
DTG	Dolutegravir
EC	Ethics committee
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
EMEA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration

FDC	Fixed-dose combination
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GMR	Geometric Mean Ratio
GSK	GlaxoSmithKline
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
h/hr	Hour(s)
HRT	Hormone Replacement Therapy
HSR	Hypersensitivity Reaction
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
kg	Kilogram
LDH	Lactate dehydrogenase
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MHRA	Medicines and Healthcare products Regulatory Agency
mg	Milligrams
mL	Milliliter
MSDS	Material Safety Data Sheet
msec	Milliseconds
NRTI	Nucleoside reverse transcriptase inhibitors
OCT	Organic cation transporter
PI	Principal investigator
PK	Pharmacokinetic(s)
PTS	Platform Technology and Science
QTc	QT duration corrected for heart rate
QTcF	QT correction using Fridericia Formula
R&D	Research and Development
RAP	Reporting and Analysis Plan
RBC	Red blood cells
RNA	Ribonucleic acid
SAE	Serious adverse event(s)
SAS	Statistical Analysis Software

SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SJS	Stevens-Johnson syndrome
SOP	Standard Operating Procedure
SRM	Study Reference Manual
SUSAR	Suspected unexpected serious adverse reactions
t	Time of last quantifiable concentration
$t_{½}$	Terminal elimination phase half-life
TEN	Toxic epidermal necrolysis
t_{lag}	Plasma DTG lag time for absorption
t_{max}	Time of occurrence of C_{max}
ULN	Upper limit of normal
UK	United Kingdom
UPLC-MS/MS	Ultra-performance liquid chromatography triple quadrapole mass spectrometry
US / USA	United States (of America)
WBC	White blood cells
WOCBP	Women of Child Bearing Potential
Vz/F	Apparent Volume of Distribution During Terminal Phase
λz	Terminal Rate Constant

Trademark Information

Trademarks of ViiV Healthcare
TIVICAY

Trademarks not owned by ViiV Healthcare
SAS

11.10. Appendix 10: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).