Protocol

Study ID: 216149

Official Title of Study: A Randomized, 2-Cohort, 2-Period, Single Dose, Crossover Clinical Study to Assess the Effect of Food on the Pediatric Dispersible Tablet Formulations of TRIUMEQ (Dolutegravir/Abacavir/Lamivudine) and DOVATO (Dolutegravir/Lamivudine) in Healthy Adult Participants

Date of Document: 04-MAR-2021

TITLE PAGE

Protocol Title: A Randomized, 2-Cohort, 2-Period, Single Dose, Crossover Clinical Study to Assess the Effect of Food on the Pediatric Dispersible Tablet Formulations of TRIUMEQ (Dolutegravir/Abacavir/Lamivudine) and DOVATO (Dolutegravir/Lamivudine) in Healthy Adult Participants

Protocol Number: 216149

Compound Number or Name:	GSK2619619 (Dolutegravir/Abacavir/Lamivudine) and GSK3515864 (Dolutegravir/Lamivudine)

Brief Title: A Food-Effect Study of the Pediatric Dispersible Tablet Formulations of TRIUMEQ and DOVATO in Healthy Adult Participants

Study Phase: Phase 1 (Food-Effect 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

Regulatory Agency Identifying Number(s):

TRIUMEQ IND: 114,820
DOVATO IND: 127,475

Approval Date: 04-MAR-2021

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 Senior Vice President, Head of Research & Development.

This study is sponsored by ViiV Healthcare. GlaxoSmithKline (PPD Inc. with GlaxoSmithKline) is supporting ViiV Healthcare in the conduct of this study.

SPONSOR SIGNATORY:

Protocol Title: A Randomized, 2-Cohort, 2-Period, Single Dose, Crossover Clinical Study to Assess the Effect of Food on the Pediatric Dispersible Tablet Formulations of TRIUMEQ (Dolutegravir/Abacavir/Lamivudine) and DOVATO (Dolutegravir/Lamivudine) in Healthy Adult Participants

Protocol Number: 216149

Compound Number or Name:	GSK2619619 (Dolutegravir/Abacavir/Lamivudine) and GSK3515864 (Dolutegravir/Lamivudine)

Sherene Min MD,
Vice President,
Head of Development

Date

The signed page is a separate document

Medical Monitor Name and Contact Information can be found in the Study Reference Manual

TABLE OF CONTENTS

PAGE

TITLE PAGE 1

SPONSOR SIGNATORY: 2

TABLE OF CONTENTS 3

1. PROTOCOL SUMMARY 6
   - 1.1. Synopsis 6
   - 1.2. Schema 9
   - 1.3. Schedule of Activities 10

2. INTRODUCTION 13
   - 2.1. Study Rationale 13
   - 2.2. Background 13
   - 2.3. Benefit/Risk Assessment 14
     - 2.3.1. Risk Assessment 15
     - 2.3.2. Benefit Assessment 18
     - 2.3.3. Overall Benefit: Risk Conclusion 18

3. OBJECTIVES AND ENDPOINTS 18

4. STUDY DESIGN 19
   - 4.1. Overall Design 19
   - 4.2. Scientific Rationale for Study Design 20
   - 4.3. Justification for Dose 20
   - 4.4. End of Study Definition 21

5. STUDY POPULATION 21
   - 5.1. Inclusion Criteria 21
   - 5.2. Exclusion Criteria 23
   - 5.3. Lifestyle Considerations 25
     - 5.3.1. Meals and Dietary Restrictions 25
     - 5.3.2. Caffeine, Alcohol, and Tobacco 25
     - 5.3.3. Activity 26
   - 5.4. Screen Failures 26
   - 5.5. Criteria for Temporarily Delaying 26

6. STUDY INTERVENTION AND CONCOMITANT THERAPY 27
   - 6.1. Study Interventions Administered 27
     - 6.1.1. Dosing Instructions for TRIUMEQ and DOVATO Dispersible Tablets 27
   - 6.2. Preparation/Handling/Storage/Accountability 28
   - 6.3. Measures to Minimize Bias: Randomization and Blinding 28
   - 6.4. Study Intervention Compliance 28
   - 6.5. Dose Modification 29
   - 6.6. Continued Access to Study Intervention after the End of the Study 29
   - 6.7. Treatment of Overdose 29
   - 6.8. Concomitant Therapy 29

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 30
7.1. Discontinuation of Study Intervention 30
7.1.1. Liver Chemistry Stopping Criteria 30
7.1.2. QTc Stopping Criteria 31
7.2. Participant Discontinuation/Withdrawal from the Study 31
7.3. Lost to Follow-up 32

8. STUDY ASSESSMENTS AND PROCEDURES 32
8.1. Efficacy Assessments 33
8.2. Safety Assessments 33
8.2.1. Physical Examinations 33
8.2.2. Vital Signs 33
8.2.3. Electrocardiograms 33
8.2.4. Clinical Safety Laboratory Assessments 34
8.2.5. Pregnancy Testing 34
8.2.6. Palatability Assessment 34
8.2.7. Toxicity Management 34
8.2.8. COVID-19 Measures 35
8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting 35
8.3.1. Time Period and Frequency for Collecting AE and SAE Information 35
8.3.2. Method of Detecting AEs and SAEs 36
8.3.3. Follow-up of AEs and SAEs 36
8.3.4. Regulatory Reporting Requirements for SAEs 36
8.3.5. Pregnancy 36
8.4. Pharmacokinetics 37
8.5. Genetics and/or Pharmacogenomics 37
8.6. Biomarkers 37
8.7. Immunogenicity Assessments 37
8.8. Medical Resource Utilization and Health Economics 37

9. STATISTICAL CONSIDERATIONS 37
9.1. Statistical Hypotheses 37
9.2. Sample Size Determination 38
9.2.1. Sample Size Assumption 38
9.2.2. Sample Size Sensitivity 38
9.3. Analysis Sets 38
9.4. Statistical Analyses 39
9.4.1. Pharmacokinetic Analysis 39
9.4.2. Safety Analysis 41
9.4.3. Other Analysis 41
9.5. Interim Analysis 41

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 42
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 42
10.1.1. Regulatory and Ethical Considerations 42
10.1.2. Financial Disclosure 42
10.1.3. Informed Consent Process 43

10.1.4. Data Protection 43
10.1.5. Committees Structure 44
10.1.6. Dissemination of Clinical Study Data 44
10.1.7. Data Quality Assurance 44
10.1.8. Source Documents 45
10.1.9. Study and Site Start and Closure 46
10.1.10. Publication Policy 46
10.2. Appendix 2: Clinical Laboratory Tests 48
10.3. Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting 50
10.3.1. Definition of AE 50
10.3.2. Definition of SAE 51
10.3.3. Recording and Follow-up of AE and SAE 52
10.3.4. Reporting of Serious Adverse Events to VH/GSK 54
10.4. Appendix 4: Contraceptive and Barrier Guidance 56
10.4.1. Definitions: 56
10.4.2. Contraception Guidance: 57
10.5. Appendix 5: Liver Safety: Required Actions and Follow-up Assessments 59
10.6. Appendix 6: Clinical Protocol COVID-19: Recommended Measures Pandemic and Clinical Trial Continuity 61
10.6.1. Study Procedures During COVID-19 Pandemic 61
10.7. Appendix 7: Toxicity Management 62
10.7.1. Specific Toxicities/Adverse Event Management 63
10.8. Appendix 8: Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Corrected Version 2.1, July 2017 67
10.9. Appendix 9: Abbreviations and Trademarks 68

11. REFERENCES 70

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Randomized, 2-Cohort, 2-Period, Single Dose, Crossover Clinical Study to Assess the Effect of Food on the Pediatric Dispersible Tablet Formulations of TRIUMEQ (Dolutegravir/Abacavir/Lamivudine) and DOVATO (Dolutegravir/Lamivudine) in Healthy Adult Participants.

Brief Title: A Food-Effect Study of the Pediatric Dispersible Tablet Formulations of TRIUMEQ and DOVATO in Healthy Adult Participants

Rationale: This study will assess the effect of food on the pharmacokinetics (PK) of TRIUMEQ (dolutegravir [DTG] 5 mg/abacavir [ABC] 60 mg/lamivudine [3TC] 30 mg) dispersible tablets developed for pediatric populations and DOVATO (dolutegravir DTG 5 mg/3TC 30 mg) dispersible tablets developed for pediatric populations. In addition, this study will assess the safety and tolerability of TRIUMEQ (DTG 5 mg/ABC 60 mg/3TC 30 mg) dispersible tablets and DOVATO (DTG 5 mg/3TC 30 mg) dispersible tablets developed for pediatric populations.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the effect of food (fasted and high-fat meal) on the PK of TRIUMEQ (DTG/ABC/3TC) dispersible tablets	• AUC(0-inf), AUC(0-t) and Cmax for TRIUMEQ (DTG/ABC/3TC)
• To assess the effect of food (fasted and high-fat meal) on the PK of DOVATO (DTG/3TC) dispersible tablets	• AUC(0-inf), AUC(0-t) and Cmax for DOVATO (DTG/3TC)
Secondary	
• To assess the effect of food (fasted and high-fat meal) on the secondary PK parameters of TRIUMEQ (DTG/ABC/3TC) dispersible tablets	• tlag, t1/2, AUC(0-24), Ct, C24 and Tmax for TRIUMEQ (DTG/ABC/3TC)
• To assess the effect of food (fasted and high-fat meal) on the secondary PK parameters of DOVATO (DTG/3TC) dispersible tablets	• tlag, t1/2, AUC(0-24), Ct, C24 and Tmax for DOVATO (DTG/3TC)
• To assess the safety and tolerability of TRIUMEQ (DTG/ABC/3TC) dispersible tablets under fasted or fed (high-fat) conditions	• Safety and tolerability endpoints include incidence of AEs and SAEs, observed and change from baseline in clinical laboratory assessments, ECGs, and vital sign

Objectives	Endpoints
• To assess the safety and tolerability of DOVATO (DTG/3TC) dispersible tablets under fasted or fed (high-fat) conditions	measurements (blood pressure and pulse rate)
Exploratory	
• To evaluate the palatability of the dispersible tablets	• Palatability questionnaire

3TC = lamivudine; ABC = abacavir; AE = adverse event; AUC(0-24) = area under the plasma concentration-time curve from time zero to 24 hours; AUC(0-inf) = area under the plasma concentration-time curve from time zero extrapolated to infinity; AUC0-t = area under the plasma concentration-time curve from time zero to time of last quantifiable concentration; C24 = concentration at 24 hours postdose; Cmax = maximum observed plasma concentration; Ct = last quantifiable concentration; DTG = dolutegravir; ECG = electrocardiogram; PK = pharmacokinetics; SAE = serious adverse event; t1/2 = terminal elimination phase half-life; tlag = lag time for absorption; Tmax = time of maximum observed concentration

Overall Design: This is a 2-cohort, single-center, randomized, open-label, single-dose, crossover study to assess the effect of food on the PK of the pediatric formulations of TRIUMEQ (DTG/ABC/3TC) dispersible tablets and DOVATO (DTG/3TC) dispersible tablets in healthy adult participants.

The study will consist of a screening period, 2 treatment periods with a single dose of study intervention per treatment period per cohort, a washout period, and a follow-up visit. Participants will have a screening visit within 28 days before the first dose of study intervention.

In each cohort, prior to dosing on Day 1 of Period 1, participants will be randomly assigned to 1 of 2 treatment sequences (AB or BA in Cohort 1 and CD or DC in Cohort 2). Cohorts are independent of one another and may run in parallel.

To ensure adequate washout, there will be at least 7 days between each dose of study intervention, with an allowance window of 4 hours (i.e., 7 days minus 4 hours) to allow flexibility in scheduling participants for dosing at the clinic.

Pharmacokinetic blood samples for the analysis of DTG, ABC, and 3TC will be collected within 60 minutes prior to dosing (0 hour) on Day 1 and up to 72 hours postdose in Periods 1 and 2.

Safety and tolerability will be assessed by monitoring and recording of adverse events (AEs) and serious AEs (SAEs), clinical laboratory test results, vital sign measurements, 12-lead electrocardiogram (ECG) results, and physical examination findings.

In each of the 2 treatment periods, participants will be admitted to the clinic up to 48 hours prior to dosing and will be discharged following completion of the last study procedure on Day 4 of each period. Participants will return to the clinic for a follow-up visit 7 to 14 days after the last dose of study intervention in Period 2.

Brief Summary: The purpose of this study is to assess the effect of food on the PK of the pediatric formulations of TRIUMEQ or DOVATO in normal healthy adult participants. Study details include:

- Total study duration for each cohort: 51 days (including screening)
- Treatment duration: 2 days (Day 1 of each period)
- Visit frequency: Follow-up visit 7 to 14 days after the last dose of study intervention in Period 2.

Number of Participants: Per cohort, approximately 16 participants will be randomized to receive and be treated with study intervention to ensure that 14 evaluable participants complete the study in each cohort.

Intervention Groups and Duration: In each cohort, participants will receive a single dose of each of the following study interventions, administered as 1 treatment per period, according to their assigned sequence:

- Cohort 1:

- Treatment A: Pediatric TRIUMEQ (DTG 5 mg/ABC 60 mg/3TC 30 mg, 6 dispersible tablets) administered as a dispersion and taken immediately under fed conditions.
- Treatment B: Pediatric TRIUMEQ (DTG 5 mg/ABC 60 mg/3TC 30 mg, 6 dispersible tablets) administered as a dispersion and taken immediately under fasted conditions.

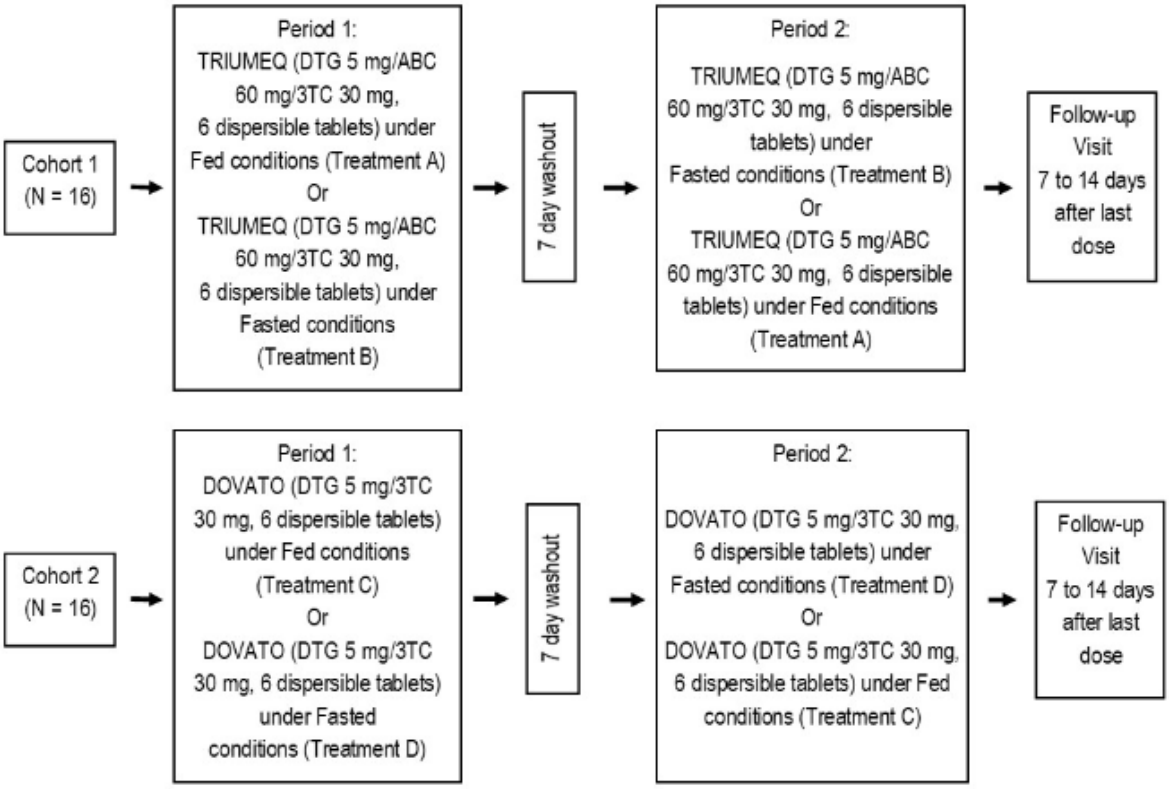
Cohort 2:

- Treatment C: Pediatric DOVATO (DTG 5 mg/3TC 30 mg, 6 dispersible tablets) administered as a dispersion and taken immediately under fed conditions.
- Treatment D: Pediatric DOVATO (DTG 5 mg/3TC 30 mg, 6 dispersible tablet) administered as a dispersion and taken immediately under fasted conditions.

    - Participants administered Treatments A and C will fast overnight for at least 10 hours prior to dosing and will receive a high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal 30 minutes prior to dosing. Dose administration will occur within 5 minutes of completion of meal consumption. Participants will not receive any further food until 4 hours after dosing.
    - Participants administered Treatments B and D will fast overnight for at least 10 hours prior to dosing and until 4 hours after dosing.

Data Monitoring/ Other Committee: No

1.2. Schema



3TC = lamivudine; ABC = abacavir; DTG = dolutegravir.
Washout will be at least 7 days minus 4 hours.

1.3. Schedule of Activities

- Screening procedures may be done over more than 1 visit but must all be completed within 28 days prior to the first dose of study intervention.
- The following demographic parameters will be captured: year of birth, sex, race, and ethnicity.
- Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria.

Screening Visit

Procedure	**Screening (Day -28 to -2)**
Informed consent	X
Inclusion and exclusion criteria	X
Demographics	X
Full physical examination including height, weight, and body mass index[1]	X
Laboratory assessments (hematology, chemistry, urinalysis)	X
Human leukocyte antigen (HLA)-B*5701	X
12-lead electrocardiogram	X
Vital sign measurements	X
Medication/drug/alcohol history	X
Past and current medical conditions	X
Pregnancy test	X
Follicle-stimulating hormone (as needed, to confirm postmenopausal status)	X
Molecular test for SARS-CoV-2[2]	X
Drug, alcohol, and cotinine screen	X
Human immunodeficiency virus, hepatitis B and hepatitis C screening	X

1 A full physical examination will include at a minimum, assessments of the skin, lungs, cardiovascular system, respiratory, gastrointestinal, abdomen (liver and spleen), and neurological systems.

2 Two consecutive approved molecular tests (polymerase chain reaction or antigen test). The first test should be performed ≥7 days prior to admission.

Treatment Period Assessments - Cohort 1 and Cohort 2

Procedure / Assessments	All Study Periods: Day –2 or Day –1[2]	Day 1	Washout[1]: Day 2	Day 3	Day 4	Follow-up/Early Discontinuation	Notes
Admit to clinic	X						Day -1 of Period 2 may be the same day as Day 6 of Period 1.
Discharge from clinic					X		Discharge from the study site following completion of the last study procedure on Day 4 of each period.
Outpatient visit[3]						X	
Brief physical examination	X						Brief physical examinations may be completed as a full physical examinations at the discretion of the investigator. See Section 8.2.1 for description of brief physical examination.
Vital signs	X				X	X	Single vital sign measurements at all time points (Section 8.2.2).
12-lead ECG	X				X		Single ECG measurements. Additional ECGs may be performed at the discretion of the investigator.
Urine drug, alcohol, and cotinine screen	X						See Appendix 2 for specific tests to be performed.
Clinical laboratory assessments[5]	X				X	X	See Section 8.2.4 for additional information and Appendix 2 for specific tests to be performed.
Molecular test for SARs-CoV-2[6]	X						Polymerase Chain Reaction (PCR) or Antigen test.
Pregnancy test	X					X	Pregnancy test will be performed as per the standard practice of the study site.
Dosing with study intervention[7]		X					
Palatability assessment		X					To be completed within 10 minutes following dosing (see Section 8.2.6)
Meals		Standard for the study site					See Section 4.1 for specific information on meals.
Serial PK sampling[8]		X	X	X	X		
AE and SAE review[8]	←==========X==========→						
Concomitant medications	←==========X==========→						

3TC = lamivudine; ABC = abacavir; AE = adverse event; DTG = dolutegravir; ECG = electrocardiogram; PK = pharmacokinetic; SAE = serious adverse event.

1. To ensure adequate washout, there will be at least 7 days between each dose of study intervention, with an allowance window of 4 hours (i.e., 7 days minus 4 hours).
2. Participants will be admitted to the study site up to 48 hours prior to dosing.
3. Follow-up visit will occur 7 to 14 days after the last dose of study intervention.
   At follow-up, male participants with no ongoing AEs or vital sign/clinical laboratory results of clinical concern may be followed up virtually by the site via telephone contact. Female participants must return for a pregnancy test.
4. Follow-up assessments should be completed in the event of an early participant discontinuation.
5. Clinical laboratory assessment at follow-up is only necessary if a participant had a previous abnormal clinical laboratory value.
6. The first test should be performed ≥7 days prior to admission. The second test should be performed 24 hours prior to admission to the unit. Participants should be quarantined within the unit until the second test result is negative. Once the test result is confirmed to be negative, participants can be released into the unit and will follow infection control practices.
7. Dosing will occur at Hour 0 on Day 1 of each period.
   Treatment A: Pediatric TRIUMEQ (DTG 5 mg/ABC 60 mg/3TC 30 mg, 6 dispersible tablets) administered as a dispersion and taken immediately under fed conditions.
   Treatment B: Pediatric TRIUMEQ (DTG 5 mg/ABC 60 mg/3TC 30 mg, 6 dispersible tablets) administered as a dispersion and taken immediately under fasted conditions.
   Treatment C: Pediatric DOVATO (DTG 5 mg/3TC 30 mg, 6 dispersible tablets) administered as a dispersion and taken immediately under fed conditions.
   Treatment D: Pediatric DOVATO (DTG 5 mg/3TC 30 mg, 6 dispersible tablets) administered as a dispersion and taken immediately under fasted conditions.
8. Blood collection for PK analysis of DTG, ABC, and/or 3TC will be collected within 60 minutes prior to dosing (0 hour) and 0.25, 0.50, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4 (prior to provision of food), 5, 6, 8, 12, 24, 48, and 72 hours post dose in each period.
9. See Section 8.3 for details for AE and SAE time periods and reporting.

- The timing and number of planned study assessments, including safety, PK, or other 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 Institutional Review Board/Independent Ethics Committee 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. The changes will be approved by the competent authorities and the ethics committee before implementation.

2. INTRODUCTION

TRIUMEQ™ (GSK2619619) is a fixed-combination (FDC) that contains the integrase inhibitor (INI) dolutegravir (DTG) (TIVICAY™, [GSK Document Number RM2007/00683/14]) and 2 nucleoside reverse transcriptase inhibitors, abacavir (ABC) and lamivudine (3TC) first approved in the US in 2014 [TRIUMEQ, 2014].

DOVATO™ (GSK3515864) is a fixed-dose combination (FDC) 2-drug regimen that contains the INI DTG [TIVICAY, [GSK Document Number RM2007/00683/14]) and the nucleoside reverse transcriptase inhibitor 3TC first approved in the US in 2019 [DOVATO, 2019].

2.1. Study Rationale

A dispersible tablet formulation (5-mg tablet for oral suspension) of TIVICAY has been developed and approved for administration in the younger pediatric populations aged ≥4 weeks and weighing at least 3 kg.

Both TRIUMEQ and DOVATO are FDC tablets and cannot be adjusted. The development of a pediatric dispersible tablet formulation of the 2-drug and 3-drug regimen, respectively, which achieves drug exposures similar to that of approved adult formulations, would be beneficial to patients weighing less than 25 kg who are not able to swallow tablet formulations. Both TRIUMEQ and DOVATO dispersible table formulations have been developed, including use of the TRIUMEQ dispersible formulation in a current clinical study.

This study will assess the effect of food on the pharmacokinetics (PK) of TRIUMEQ (DTG 5 mg/abacavir [ABC] 60 mg/3TC 30 mg) dispersible tablets (6 dispersible tablets to achieve DTG 30 mg/ABC 360 mg/3TC 180 mg) and DOVATO (DTG 5 mg/3TC 30 mg) dispersible tablets (6 dispersible tablets to achieve DTG 30 mg/3TC 180 mg), both being developed for pediatric populations. In addition, this study will assess the safety and tolerability of DOVATO (DTG 5 mg/3TC 30 mg) (6 dispersible tablets to achieve DTG 30 mg/3TC 180 mg) dispersible tablets and TRIUMEQ (DTG 5 mg/ABC 60 mg/3TC 30 mg) (6 dispersible tablets to achieve DTG 30 mg/ABC 360 mg/3TC 180 mg) dispersible tablets.

This study will be conducted in accordance with the Food and Drug Administration (FDA) guidance for industry on food-effect bioavailability and fed bioequivalence studies [Department of Health and Human Services [DHHS, 2002].

2.2. Background

TIVICAY, as a DTG single-drug entity, is a next generation INI with low to moderate inter-participant PK variability, a predictable exposure-response relationship, and a 14-hour plasma half-life that supports once-daily dosing without the need for PK boosters.

Fixed-dose combinations have greatly simplified the treatment of patients with human immunodeficiency virus (HIV). The promise of improved adherence is important; FDCs

potentially allow simplification of dosing and can reduce pill burden. Adherence to therapy is essential to achieve viral suppression and prevent emergence of resistance mutations. Among regimens of comparable efficacy, physicians and HIV-1-infected patients who receive antiretroviral therapy (ART) rate total pill burden, dosing frequency, and safety concerns among the greatest obstacles to achieving adherence. Drug resistant virus eventually emerges in most patients who struggle with consistent adherence. To achieve successful long-term treatment, the prevention of drug resistance has become the most significant challenge.

DOVATO is a two-drug, FDC tablet. The combination of DTG, with its high barrier to resistance and ability to confer a rapid decline in HIV-1 ribonucleic acid (RNA), with the nucleoside reverse transcriptase inhibitor 3TC, has shown a low frequency of virologic failure and emergent resistance comparable with other currently available three-drug regimens. The efficacy and safety of the two-drug FDC of DOVATO makes it suitable for both treatment-naïve individuals, and as a replacement treatment for three-drug ART in virologically suppressed ("switch") patients [DOVATO, 2019].

TRIUMEQ is a three-drug FDC tablet developed to address the need for a FDC with an integrase strand transfer inhibitor paired with a dual nucleoside reverse transcriptase inhibitor backbone (ABC/3TC) and is now approved for the treatment of HIV in adults and pediatric patients weighing at least 40 kg as a single-tablet regimen with or without food to achieve convenient dosing and improve patient compliance.

Alternate formulations (e.g., dispersible tablets) and dosing strategies for both DOVATO and TRIUMEQ have been developed for pediatric patients less than 12 years old who may have difficulty swallowing conventional tablet formulations.

A detailed description of the chemistry, pharmacology, efficacy, and safety of DTG as a single entity, in combination with ABC/3TC as TRIUMEQ, and in combination with 3TC as DOVATO, is provided in the Clinical Investigator's Brochure (CIB) [GSK Document Number RM2007/00683/14] and the prescribing information TIVICAY, 2013; DOVATO, 2019;TRIUMEQ, 2014].

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of DTG, ABC, and 3TC may be found in the CIB [GSK Document Number RM2007/00683/14] and the prescribing information [DOVATO, 2019; TRIUMEQ, 2014].

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy[1]
Refer to the full prescribing information for additional information on TRIUMEQ (DTG/ABC/3TC) Refer to the full prescribing information for additional information on DOVATO (DTG/3TC)		
Hypersensitivity (including ABC hypersensitivity reaction) and rash	A well characterized, idiosyncratic, drug-related hypersensitivity reaction is the most important risk associated with ABC (Section 10.7.1.3). Exclusion of individuals found to carry the *human leukocyte antigen (HLA)-B*5701* allele from ABC therapy reduces the risk of hypersensitivity reaction. Rash, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme have been reported in patients taking ABC (Section 10.7.1.4). Hypersensitivity reactions have 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, toxic epidermal necrolysis, and erythema multiforme were reported. Data on hypersensitivity reactions for DTG and DTG+ABC/3TC FDC suggest that there will not be additional risk from hypersensitivity reactions in *HLA-B*5701* negative participants receiving the DTG/ABC/3TC FDC.	• Participants must be negative for *HLA-B*5701* for inclusion in the study (Section 5.1). Additionally, participants with history of allergy/sensitivity to any of the study interventions are excluded (Section 5.2). • Specific/detailed toxicity management guidance is provided for suspected hypersensitivity reactions with DTG or ABC (Appendix 7), and skin reactions without systemic involvement (Appendix 7). • The participant informed consent form includes information on this risk and the actions participants should take in the event of a hypersensitivity reaction or associated signs and symptoms. • Participants in Cohort 2 will be provided with an ABC hypersensitivity reaction warning card and are to be reminded to read it.
Drug induced liver injury (DILI) and other clinically significant liver chemistry elevations	Nonclinical data suggested a possible, albeit low, risk for hepatobiliary toxicity with DTG. Drug-related hepatitis is considered an uncommon risk for ART containing DTG regardless of dose or treatment population. Current treatment guidelines do not recommend mono therapy with 3TC for patients with hepatitis B virus (HBV) infection, which is what participants randomly assigned to DTG/ABC/3TC would effectively be receiving. Additionally, discontinuation of 3TC in HBV infected participants can result in severe exacerbations of HBV.	Participants meeting exclusion criteria 6, 7, 9, and/or 10 during the screening period are excluded from participating (Section5.2). Specific/detailed liver chemistry stopping criteria (Section 7.1.1) and toxicity management guidance is provided for suspected DILI or other clinically significant liver chemistry elevations (Appendix 5).
Theoretical serious drug interaction with dofetilide	Co-administration of DTG may increase dofetilide plasma concentration via inhibition of organic cation transporter 2 transporter, resulting in potentially life-threatening toxicity.	Concomitant medications (e.g., dofetilide) are prohibited in the study (Section 5.2 and Section 6.8).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy[1]
Gastrointestinal (GI) intolerance	Nonclinical studies showed upper and lower GI toxicity, including vomiting, diarrhea, and gastric erosions observed in monkey toxicology studies (thought to be related to local and not systemic toxicity). Mild to moderate GI intolerance (mainly diarrhea and nausea) is associated with DTG treatment in a small proportion of participants; however, there were no indications of an increased risk for peptic ulcers or serious erosions.	Routine monitoring of GI symptoms will be performed (Section 8.3 and Appendix 3).
Renal function	Mild elevations of creatinine have been observed with DTG that are related to a benign effect on creatinine secretion with blockade of the OCT-2 receptor. DTG has been shown to have no significant effect on glomerular filtration rate (GFR) or effective renal plasma flow. Measurement of albumin/creatinine ratio confirmed there was no difference in the effect of DTG on albumin excretion compared with EFV or Raltegravir (RAL). 3TC is eliminated by renal excretion and exposure increases in patients with renal dysfunction.	Due to requirements for dose reduction of 3TC in patients with renal dysfunction, participants with a creatinine clearance <90 mL/min are excluded (Section 5.2). Specific/detailed toxicity management guidance is provided for participants who develop a decline in renal function (Appendix 5). Increases in serum creatinine 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 in this protocol for DTG.
Psychiatric disorders	Psychiatric disorders including suicide ideation and behaviors are common in HIV-infected patients. The psychiatric profile for DTG (including suicidality, depression, bipolar and hypomania, anxiety, and abnormal dreams) was similar or favorable compared with other ARVs. The reporting rate for insomnia was statistically higher for blinded DTG+ABC/3TC compared with EFV/TDF/FTC in ING114467; however, this was not duplicated in any other Phase IIb/III study conducted with DTG.	This study is limited to healthy volunteers only (Section 5.1).
Creatine phosphokinase (CPK) elevations	Asymptomatic CPK elevations mainly in association with exercise have been reported with DTG therapy.	Specific detailed toxicity management guidance is provided for participants who develop Grade 3 to 4 CPK elevations (Appendix 5).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy[1]
Use in pregnancy	The safe use of DTG in human pregnancy has not been established. DTG has been shown to cross the placenta in reproductive toxicity studies in animals. DTG has not been associated with findings in animal reproductive studies.	Women who are pregnant will be excluded from the study (Section 5.2). Females of childbearing potential are required to have a negative pregnancy test at both screening and Day 1 of the study and agree to use one of the methods documented in Appendix 4 to avoid pregnancy during the study. Pregnant women will be withdrawn from this study and their pregnancy followed to determine outcome (including premature termination) and status of mother and child.

1. 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 [Appendix 8]). Serious/severe events will be managed appropriately including, but not limited to, withdrawal of study intervention 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 the pediatric formulations of TRIUMEQ and DOVATO. Participation in this study may contribute to the process of developing new formulations for the treatment of HIV. There may be benefit to individual participants from the medical evaluations and assessments that could identify conditions that the participant was previously unaware of.

2.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize the risk to participants in this study, the potential risks identified in association with TRIUMEQ and DOVATO are low.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To assess the effect of food (fasted and high-fat meal) on the PK of TRIUMEQ (DTG/ABC/3TC) dispersible tablets	• AUC(0-inf), AUC(0-t) and Cmax for TRIUMEQ (DTG/ABC/3TC)
• To assess the effect of food (fasted and high-fat meal) on the PK of DOVATO (DTG/3TC) dispersible tablets	• AUC(0-inf), AUC(0-t) and Cmax for DOVATO (DTG/3TC)
Secondary	
• To assess the effect of food (fasted and high-fat meal) on the secondary PK parameters of TRIUMEQ (DTG/ABC/3TC) dispersible tablets	• tlag, t1/2, AUC(0-24), Ct, C24 and Tmax for TRIUMEQ (DTG/ABC/3TC)
• To assess the effect of food (fasted and high-fat meal) on the secondary PK parameters of DOVATO (DTG/3TC) dispersible tablets	• tlag, t1/2, AUC(0-24), Ct, C24 and Tmax for DOVATO (DTG/3TC)
• To assess the safety and tolerability of TRIUMEQ (DTG/ABC/3TC) dispersible tablets under fasted or fed (high-fat) conditions • To assess the safety and tolerability of DOVATO (DTG/3TC) dispersible tablets under fasted or fed (high-fat) conditions	• Safety and tolerability endpoints include incidence of AEs and SAEs, observed and change from baseline in clinical laboratory assessments, ECGs, and vital sign measurements (blood pressure and pulse rate)
Exploratory	
• To evaluate the palatability of the dispersible tablets	• Palatability questionnaire

3TC = lamivudine; ABC = abacavir; AE = adverse event; AUC(0-24) = area under the plasma concentration-time curve from time zero to 24 hours; AUC(0-inf) = area under the plasma concentration-time curve from time zero extrapolated to infinity; AUC0-t = area under the plasma concentration-time curve from time zero to time of last quantifiable concentration; C24 = concentration at 24 hours postdose; Cmax = maximum observed plasma concentration; Ct = last

quantifiable concentration; DTG = dolutegravir; ECG = electrocardiogram; PK = pharmacokinetics; SAE = serious adverse event; t1/2 = terminal elimination phase half-life; tlag = lag time for absorption; Tmax = time of maximum observed concentration; Vz/F = apparent volume of distribution.

4. STUDY DESIGN

4.1. Overall Design

This is a 2-cohort, single-center, randomized, open-label, single-dose, crossover study to assess the effect of food on the PK of the pediatric formulations of TRIUMEQ (DTG/ABC/3TC) dispersible tablets and DOVATO (DTG/3TC) dispersible tablets in healthy adult participants.

The study will consist of a screening period, 2 treatment periods with a single dose of study intervention per treatment period in each cohort, a washout period, and a follow-up visit. Participants will have a screening visit within 28 days before the first dose of study intervention.

In each cohort, prior to dosing on Day 1 of Period 1, participants will be randomly assigned to 1 of 2 treatment sequences (AB or BA in Cohort 1 and CD or DC in Cohort 2). Cohorts are independent of one another and may run in parallel.

Cohort 1:

- Treatment A: Pediatric TRIUMEQ (DTG 5 mg/ABC 60 mg/3TC 30 mg, 6 dispersible tablets) administered as a dispersion and taken immediately under fed conditions.
- Treatment B: Pediatric TRIUMEQ (DTG 5 mg/ABC 60 mg/3TC 30 mg, 6 dispersible tablets) administered as a dispersion and taken immediately under fasted conditions.

Cohort 2:

- Treatment C: Pediatric DOVATO (DTG 5 mg/3TC 30 mg, 6 dispersible tablets) administered as a dispersion and taken immediately under fed conditions.
- Treatment D: Pediatric DOVATO (DTG 5 mg/3TC 30 mg, 6 dispersible tablets) administered as a dispersion and taken immediately under fasted conditions.

To ensure adequate washout, there will be at least 7 days between each dose of study intervention, with an allowance window of 4 hours (i.e., 7 days minus 4 hours) to allow flexibility in scheduling participants for dosing at the clinic.

Participants administered Treatments A and C will fast overnight for at least 10 hours prior to dosing and will receive a high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal 30 minutes prior to dosing (Section 6.1.1) per the Food and Drug Administration (FDA) guidance for industry on food-effect bioavailability and fed bioequivalence studies [DHHS, 2002]. Dose administration will occur within 5 minutes of completion of meal consumption. Participants will not receive any further food until 4 hours after dosing.

Participants administered Treatments B and D will fast overnight for at least 10 hours prior to dosing and until 4 hours after dosing.

Pharmacokinetic blood samples for the analysis of DTG, ABC, and 3TC will be collected prior to dosing (0 hour) on Day 1 and up to 72 hours postdose in Periods 1 and 2.

Safety and tolerability will be assessed by monitoring and recording of AEs, clinical laboratory test results, vital sign measurements, 12-lead electrocardiogram (ECG) results, and physical examination findings.

Study assessments will be performed as indicated in the schedule of activities (SoA) (Section 1.3). In each of the 2 treatment periods, participants will be admitted to the study site up to 48 hours prior to dosing and will be discharged following completion of the last study procedure on Day 4 of each period. Participants will return to the study site for a follow-up visit 7 to 14 days after the last dose of study intervention in Period 2. The total duration of the study, including screening, is approximately 51 days.

4.2. Scientific Rationale for Study Design

This is an open-label, single-dose, 2-cohort, 2-period, single-center, crossover study to investigate the effect of food on the PK of the pediatric formulations of TRIUMEQ and DOVATO dispersible tablets.

The study will investigate the effect of a high-fat and high-calorie meal on the PK, safety, and tolerability of the pediatric formulations of TRIUMEQ and DOVATO dispersible tablets compared to administration under fasting conditions in accordance with the Food and Drug Administration (FDA) guidance for industry on food-effect bioavailability and fed bioequivalence studies [DHHS, 2002].

TRIUMEQ dispersible tablet is a bilayer tablet with DTG and 3TC in one layer and ABC in the other layer. DOVATO dispersible tablet formulation is a monolayer tablet. DTG and 3TC are common both in TRIUMEQ and DOVATO dispersible tablet formulations. Since both formulations are not identical, the impact of food on each of the components may be different; thus, both formulations are included in the study.

The open-label crossover design of this study is well-established for studying the effect of food. Random assignment to treatment sequences is an attempt to prevent bias. The washout of at least 7 days between each dose of study intervention should eliminate the possibility of carryover of drug exposure from the previous dose.

This study is subject to the appropriate regulatory and ethics committee approval and will be listed on the website ClinicalTrials.gov. No placebo control will be used, as this is not necessary for the purposes of this study.

4.3. Justification for Dose

The US FDA-approved dose of TRIUMEQ for the treatment of HIV infection in adults and pediatric patients weighing at least 40 kg is 1 oral tablet, once daily, with or without

food. TRIUMEQ is an FDC product containing 600 mg of ABC, 50 mg of DTG, and 300 mg of 3TC.

The US FDA-approved dose of DOVATO for the treatment of HIV infection in adults is 1 oral tablet, once daily, with or without food. DOVATO is an FDC product containing 50 mg of DTG and 300 mg of 3TC.

The US FDA has approved TIVICAY tablets and tablets for suspension for the treatment of HIV-1 infection in pediatric patients as young as 4 weeks of age and weighing at least 3 kg in combination with other ART.

The highest approved TIVICAY dose with the dispersible tablet formulation is 30 mg. The pediatric TRIUMEQ dispersible tablet dose of 30 mg DTG, 360 mg ABC, and 180 mg 3TC (6 tablets each consisting of DTG 5 mg, ABC 60 mg, and 3TC 30 mg) and the pediatric DOVATO dispersible tablet dose of 30 mg DTG and 180 3TC (6 tablets each consisting of DTG 5 mg and 3TC 30 mg) were selected for this study as these will be the highest marketed doses for the pediatric population.

4.4. End of Study Definition

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 SoA (Section 1.3) for the last participant in the study.

A participant is considered to have completed the study if he or she has completed all phases of the study including the final date on which data were or are expected to be collected.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

Age

1. Participant must be 18 to 50 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who are healthy as determined by the investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring (history and electrocardiogram [ECG]).

Weight

3. Body weight ≥50.0 kg (110 lbs) for males and ≥45 kg (99 lbs) for females and body mass index within the range 18.5 to 31.0 kg/m^2 (inclusive).

Sex

Sex and Contraceptive/Barrier Requirements

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

4. Male or female
    a. Male Participants:
        1. A male participant must agree to use contraception as detailed in Appendix 4 during the treatment period and for at least 2 weeks ***plus*** an additional 90 days (a spermatogenesis cycle) after the last dose of study intervention and refrain from donating sperm during this period.
    b. Female Participants:
        1. A female participant is eligible to participate if she is not pregnant (as confirmed by a negative serum human chorionic gonadotrophin test), not lactating or breastfeeding, and at least 1 of the following conditions applies:
            - Is not a woman of childbearing potential (WOCBP) as defined in Appendix 4.

            OR

            - Is a WOCBP and using a nonhormonal contraceptive method that is highly effective, with a failure rate of <1%, as described in Appendix 4, for 30 days before study intervention, during the treatment periods, and for at least 30 days (i.e., 5 half-lives) after the last dose of study intervention and completion of the follow-up visit. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive serum pregnancy test (Appendix 2) at screening and check-in (Day -1).
- Additional requirements for pregnancy testing during and after study intervention are outlined in Appendix 4.
- 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.

History/Diagnostic

6. Documentation that the participant is negative for the human leukocyte antigen (HLA)-B*5701 allele.

5.2. Exclusion Criteria

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

Medical Conditions

1. Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).

2. Medical history of cardiac arrhythmias, prior myocardial infarction in the past 3 months, or cardiac disease or a family or personal history of long QT syndrome.
3. A pre-existing condition interfering with normal gastrointestinal anatomy or motility (e.g., gastroesophageal reflux disease, gastric ulcers, gastritis), hepatic and/or renal function, that could interfere with the absorption, metabolism, and/or excretion of the study intervention.
4. QTcF >450 msec

   NOTES:

   - The QTc is the QT interval corrected for heart rate according to Fridericia's formula (QTcF) machine-read or manually over-read.
   - QTcF will be used to determine eligibility and discontinuation for an individual participant in this trial.
5. A participant with known or suspected active coronavirus disease (COVID-19) infection OR contact with an individual with known COVID-19, within 14 days of study enrollment.

Laboratory Assessments

6. Presence of hepatitis B surface antigen at screening or within 3 months prior to starting study intervention.
7. Positive hepatitis C antibody test result at screening or within 3 months prior to starting study intervention AND positive on reflex to hepatitis C RNA.
8. Positive HIV-1 and -2 antigen/antibody immunoassay at screening.
9. Alanine aminotransferase (ALT) >1.5 × upper limit of normal (ULN). A single repeat of ALT is allowed within a single screening period to determine eligibility.
10. Bilirubin >1.5 × ULN (isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%). A single repeat of any laboratory abnormality is allowed within a single screening period to determine eligibility.
11. Any acute laboratory abnormality at screening which, in the opinion of the investigator, should preclude participation in the study of an investigational compound.

12. Any Grade 2 to 4 laboratory abnormality at screening, with the exception of creatine phosphokinase (CPK) and lipid abnormalities (e.g., total cholesterol, triglycerides), and ALT (described above), will exclude a participant from the study unless the investigator can provide a compelling explanation for the laboratory result(s) and has the assent of the sponsor. A single repeat of any laboratory abnormality is allowed within a single screening period to determine eligibility.
13. A positive test result for drugs of abuse (including marijuana), alcohol, or cotinine (indicating active current smoking) at screening or before the first dose of study intervention.

Prior/Concomitant Therapy

14. Unable to refrain from the use of prescription or non-prescription drugs including vitamins, herbal and dietary supplements (including St John's wort) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study intervention and for the duration of the study until completion of the follow-up visit, unless, in the opinion of the investigator and ViiV Healthcare (VH)/GSK medical monitor, the medication will not interfere with the study procedures or compromise participant safety. (Note: acetaminophen at doses of ≤2 grams/day is permitted for use any time during the study.)
15. Unwillingness to abstain from excessive consumption (defined in Section 5.3.1) of any food or drink containing grapefruit and grapefruit juice, Seville oranges, blood oranges, or pomelos or their fruit juices within 7 days prior to the first dose of study intervention(s) until the end of the study.

Prior/Concurrent Clinical Study Experience

16. Participation in another concurrent clinical study or prior clinical study (with the exception of imaging trials) prior to Day 1 of Period 1 in the current study: 30 days, 5 half-lives, or twice the duration of the biological effect of the study intervention (whichever is longer).
17. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 60 days.

Diagnostic assessments

18. Estimated serum creatinine clearance (CKD-EPI) <90 mL/min.

Other Exclusions

19. History of regular alcohol consumption within 6 months of the study, defined as an average weekly intake of >14 units for males or >7 drinks for females. One unit is equivalent to 12 g of alcohol: 12 ounces (360 mL) of beer, 5 ounces (150 mL) of wine, or 1.5 ounces (45 mL) of 80 proof distilled spirits.
20. Unable to refrain from tobacco or nicotine-containing products within 1 month prior to screening.

21. History of sensitivity, prior intolerance or hypersensitivity to any of the study interventions, or components thereof, or a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates their participation.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

- Refrain from excessive consumption of red wine, grapefruit and grapefruit juice, Seville oranges, blood oranges, or pomelos or their fruit juices within 7 days prior to the first dose of study intervention until the end of the study. Excessive consumption is defined as more than one glass of wine or juice or one of these fruits per day, in combination.
- Participants will refrain from chewing or ingesting sugar-free gums, candies or other processed food/drink products that contain sugar alcohols (e.g., sorbitol, mannitol, xylitol, maltitol, isomalt) during the inpatient period of each dosing session (i.e., Day 1 through 96 hours post dose in each period).
- Once in the clinical unit, participants will not be allowed to eat anything other than the food provided by the study center.
- No water is allowed from 1 hour prior to dosing until 2 hour after dosing except for the glass of water needed to administer the study intervention (Section 6.1.1). Water is allowed ad libitum at all other times.
- The food content of meals must be identical on the Day 1 serial PK sampling for Periods 1 and 2.

5.3.1.1. Fed Conditions

- Treatments A and C will be administered in the fed state. Participants will fast overnight for at least 10 hours prior to dosing and will receive a high-fat and high-calorie meal 30 minutes prior to dosing. Participants will eat this meal in 25 minutes or less. Dose administration will occur within 5 minutes of completion of meal consumption. Participants will not receive any further food until 4 hours after dosing on serial PK sampling days (i.e., Day 1 of Periods 1 and 2). A high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal is recommended as a test meal which should derive approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively, per FDA guidance [DHHS, 2002].

5.3.1.2. Fasted Conditions

- Treatments B and D will be administered in the fasted state. Participants will fast overnight for at least 10 hours prior to dosing until 4 hours after dosing.

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 PK sample at 72 hours postdose.

- During each dosing session, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK sample at 72 hours post dose.
- Use of tobacco- and nicotine-containing products will not be allowed from 1 month prior to screening until after the final visit.
- Participants must have a negative drug test at screening and Day -1 and must abstain from recreational drug use from screening until after the final visit.

5.3.3. Activity

- Participants will abstain from strenuous exercise for 48 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, any protocol deviations, and any serious AEs (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

5.5. Criteria for Temporarily Delaying

Not applicable.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

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 Interventions Administered

Intervention Name	TRIUMEQ (DTG/ABC/3TC)	DOVATO (DTG/3TC)
Type	Drug	Drug
Dose Formulation	Dispersible Tablet	Dispersible Tablet
Unit Dose Strengths	Single dose, FDC tablet - DTG 5 mg/ABC 60 mg/3TC 30 mg	Single dose, FDC tablet - DTG 5 mg/3TC 30 mg
Dosage Level	6 dispersible tablets of DTG 5 mg/ABC 60 mg/3TC 30 mg for a total dose of 30 mg/360 mg/180 mg	6 dispersible tables of DTG 5 mg/3TC 30 mg for a total dose of 30 mg/180 mg
Route of Administration	Oral	Oral
IMP and NIMP	IMP	IMP
Sourcing	Sourced by sponsor	Sourced by sponsor
Packaging and Labelling	Study Intervention will be provided in high-density polyethylene bottles. Each bottle will be labelled as required per country requirement.	Study Intervention will be provided in high-density polyethylene bottles. Each bottle will be labelled as required per country requirement.

- 3TC = lamivudine; ABC, abacavir; DTG = dolutegravir; FDC = fixed-dose combination; IMP = investigational medicinal product

6.1.1. Dosing Instructions for TRIUMEQ and DOVATO Dispersible Tablets

- Each dispersible tablet for TRIUMEQ contains DTG 5 mg/ABC 60 mg/3TC 30 mg. Six dispersible tablets will be needed to achieve the total dose (DTG 30 mg/ABC 360 mg/3TC 180 mg).
- Each dispersible tablet for DOVATO contains DTG 5 mg/3TC 30 mg. Six dispersible tablets will be needed to achieve the total dose (DTG 30 mg/3TC 180 mg).

1. Place 20 mL of clean drinking water in a 60 mL dosing cup. A syringe is appropriate to measure this volume to ensure accuracy.

2. Place 6 tablets into the container and swirl gently for 1 to 2 minutes to disperse the tablets. Ensure the tablets have fully dispersed before moving to the next step.
3. Have the participant swallow the dispersion as swiftly as they can, preferably in 1 to 2 swallows.
4. Rinse the container with 15 mL of water (a syringe is appropriate to measure this volume to ensure accuracy) and have the participant swallow the rinse as swiftly as they can, preferably in 1 to 2 swallows.
5. Give the participant an additional 205 mL of water to swallow (Note: total volume of water given in steps 1 through 5 should be 240 mL and will be documented). Note: the words "immediately dose" in the protocol mean within 30 minutes after completion of the preparation.

6.2. Preparation/Handling/Storage/Accountability

1. 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.
2. Only participants enrolled in the study may receive study intervention and only authorized study 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.
3. The investigator, study site, 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).
4. Further guidance and information for the final disposition of unused study intervention are provided in the Study Reference Manual (SRM).
5. Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff.
6. A Material Safety Data Sheet/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 VH/GSK.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label, single-center study. Within each cohort, study participants will be randomly assigned to 1 of 2 treatment sequences in accordance to the randomization scheduled generated by PPD prior to the start of the study and using validated software.

6.4. Study Intervention Compliance

- When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.
- When participants are dosed at the study 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 study site 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 staff will examine each participant's mouth to ensure that the study intervention was ingested.

6.5. Dose Modification

Not applicable.

6.6. Continued Access to Study Intervention after the End of the Study

Participants will not receive any additional treatment from VH/GSK after completion of the study because only healthy participants are eligible for study participation.

6.7. Treatment of Overdose

For this study, any dose of TRIUMEQ greater than DTG 30 mg/ABC 360 mg/3TC 180 mg (6 tablets of DTG 5 mg/ABC 60 mg/3TC 30 mg) or DOVATO greater than DTG 30 mg/3TC 180 mg (6 tablets of DTG 5 mg/3TC 30 mg) within a 24-hour time period, will be considered an overdose.

VH/GSK does not recommend specific treatment for an overdose of TRIUMEQ or DOVATO. The investigator will use clinical judgement to treat an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until TRIUMEQ or DOVATO can no longer be detected systemically (at least 7 days).
3. Obtain a plasma sample for PK analysis within 2 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 on the printed case report form (CRF) or electronic CRF (eCRF).

Decisions regarding dose interruptions will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

6.8. 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 enrollment 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 should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking prescription or non-prescription drugs including vitamins, herbal and dietary or herbal supplements (including St John's wort) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study intervention and for the duration of the study until completion of the follow-up visit, unless, in the opinion of the investigator and VH/GSK medical monitor, the medication will not interfere with the study procedures or compromise participant safety.

Acetaminophen at doses of ≤2 grams/day is permitted for use any time during the study. Other concomitant medications may be considered on a case-by-case basis by the investigator in consultation with the VH/GSK medical monitor.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

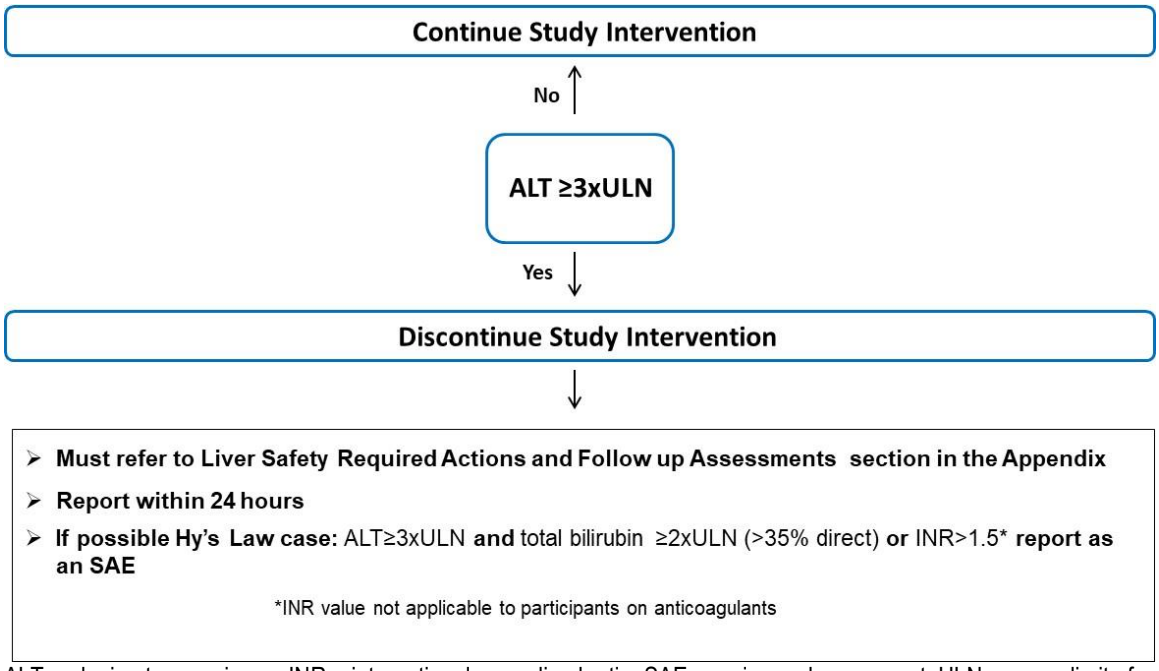
7.1. Discontinuation of Study Intervention

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 PK. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

7.1.1. Liver Chemistry Stopping Criteria

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

Figure 1 Phase 1 Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



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

Refer to Appendix 5 for required Liver Safety Actions and Follow-up Assessments.

7.1.2. QTc Stopping Criteria

The same correction formula (QTcF) 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.

- An enrolled participant that develops an on-treatment QTcF >500 msec or an increase from baseline QTcF >60 ms should have 2 repeat unscheduled ECGs within 10 minutes. Using these triplicate ECGs, if the average QTcF >500 ms or an increase from baseline QTcF >60 ms, the participant will be withdrawn from the study.
  - See the SoA (Section 1.3) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his or her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance 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 (Section 1.3). See SoA for data to be collected at the time of study discontinuation and follow-up and 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 or 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 study site for a required study visit:

- The study 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 or she will be considered to have withdrawn from the study.

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

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3).
- 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 (Section 1.3), 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 (Section 1.3).
- 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 500 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Efficacy Assessments

Not applicable.

8.2. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Physical Examinations

- A brief physical examination (screening and Day -1 of each period) will include, at a minimum, assessments of the skin, 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

- Oral temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in a supine or semi-supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceeded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones.

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 ECGs will be obtained at screening and Day -1 of each period using an ECG machine that automatically calculates the pulse rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 7.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.

8.2.4. Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- Clinical laboratory assessments at follow-up are only necessary if a participant had a previous abnormal laboratory value.
- All laboratory tests with values considered clinically significantly abnormal on Day -1, Day 4 of each period, or at the follow-up visit (if applicable) 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 clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology 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 (Section 1.3).
- If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

8.2.5. Pregnancy Testing

- Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.
- 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 at any time during the participant's involvement in the study.

8.2.6. Palatability Assessment

A palatability questionnaire will be administered to each participant within 10 minutes following dosing of dispersion treatments, as indicated in the SoA (Section 1.3). Participants will be given the questionnaire to read prior to receiving each unique dispersion dose. Details for the palatability questionnaire will be included in the SRM.

8.2.7. Toxicity Management

Both ABC and DTG are associated with a risk for hypersensitivity reactions, which were observed more commonly with ABC. Hypersensitivity reactions observed for each of these study intervention share some common features such as fever and/or rash with other symptoms indicating multiorgan involvement. Time to onset was typically 10 to 14 days for both ABC and DTG-associated reactions, although reactions to ABC may occur at any time during therapy. Additional information on toxicity management is outlined in Appendix 7.

8.2.8. COVID-19 Measures

The measures approved for implementation within this clinical trial to protect participant safety, welfare, and rights, and to ensure data integrity and the integrity of the clinical trial, as a result of COVID-19 only, are outlined in Appendix 6.

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs or SAEs can be found in Appendix 3.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

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 all AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study intervention (see Section 7).

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.

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

- All AEs and SAEs will be collected from the start of study 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 VH/GSK product will be recorded from the time a participant consents to participate in the study.
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be considered medical history, not an AE, and will be recorded in the source documents.
- 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 or 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

- Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and nonleading 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 an 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 Board (IRB)/Independent Ethics Committee (IEC), and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) 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.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.3.5. Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and through the end of the pregnancy (termination or delivery).
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to VH/GSK within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant/pregnant female partner and the neonate and the information will be forwarded to the sponsor.
- Any poststudy pregnancy-related SAEs considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.4. Pharmacokinetics

- Whole blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of DTG, ABC, and 3TC, as specified in the SoA (Section 1.3).
- Instructions for the collection and handling of biological samples will be provided in the SRM. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of DTG, ABC, 3TC. Samples collected for analyses of plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

8.5. Genetics and/or Pharmacogenomics

A sample for *HLA-B*5701* allele will be drawn at screening for qualitative inclusion/exclusion only. There will be no quantitative analysis of these samples and they will not be stored.

8.6. Biomarkers

Biomarkers are not evaluated in this study.

8.7. Immunogenicity Assessments

Immunogenicity is not evaluated in this study.

8.8. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

There is no formal hypothesis that will be statistically tested in this study. An estimation approach will be used to evaluate the effect of food on the PK of FDC dispersible tablets.

9.2. Sample Size Determination

9.2.1. Sample Size Assumption

A maximum of 16 participants per cohort will be enrolled to study intervention such that approximately 14 evaluable participants per cohort complete the study.

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Based on the results from a previous PK study of DTG granules administered to healthy participants [GSK Document Number 2017N330422_00], the within participant variability (CVw%) of DTG/ABC/3TC and DTG/3TC area under the plasma concentration-time curve (AUC) from time zero extrapolated to infinity (AUC[0-inf]), AUC from time zero to time of last observed quantifiable concentration calculated using the linear trapezoidal method when concentrations are increasing and the logarithmic trapezoidal method when concentrations are decreasing AUC(0-t), and maximum observed plasma concentration (Cmax) ranged from 4.8% and 21.4%. Therefore, it was decided that 21.4% would be a conservative estimate on which the sample size calculation is based.

For each study cohort, with a sample size of 14 evaluable participants, it is estimated that the precision (i.e., half-width of the 90% confidence interval (CI) on the ratio scale) for the test:reference comparison will be within 15.3% of the point estimate for AUC(0-inf), AUC(0-t), and Cmax. Hence, if the point estimate of the ratio of geometric means is 1, then the 90% CI will be approximately (0.87, 1.15).

9.2.2. Sample Size Sensitivity

For the sensitivity analysis, assuming a higher %CVw (30%) and a sample size of 14 evaluable participants in each study cohort, it was estimated that the half-width of the 90% CI for the ratio of treatment comparison (test:reference) would be within 21.7% of the point estimate for AUC(0-inf), AUC(0-t), and Cmax. Hence, if the point estimate of the ratio of geometric means is 1, then the 90% CI will be approximately (0.82, 1.22).

9.3. Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Screened	The Screened Population will include all participants who sign the ICF. This population will be used to present the date of first subject first screened, and numbers of subjects screened and enrolled.

Population	Description
Safety	The Safety Population will include all participants who receive at least 1 dose of study intervention. This population will be used for all demographic and safety summaries.
Pharmacokinetic Concentration	The PK Concentration Population will include all participants who undergo plasma PK sampling and have evaluable PK assay results. This population will be used for the PK concentration listings, summary tables, and plotting of concentration-time data.
Pharmacokinetic Parameter	The PK Parameter Population will include all participants who undergo plasma PK sampling and have evaluable PK parameters estimated. This population will be used for PK parameter listings, summary tables, and statistical analysis tables.

9.4. Statistical Analyses

The statistical analysis plan will be finalized prior to first patient first visit and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. Pharmacokinetic Analysis

Plasma DTG, ABC, and 3TC concentration-time data will be analyzed by PPD, under the oversight of Clinical Pharmacology Modelling & Simulation department within VH/GSK, using noncompartmental methods with Phoenix WinNonlin Version 8.0 or higher. Statistical analysis will be performed by PPD, under the oversight of Biostatistics, VH/GSK. Calculations will be based on the actual sampling times recorded during the study. From the plasma DTG, ABC, and 3TC concentration-time data, the following primary pharmacokinetic parameters will be determined and analysed: Cmax, AUC(0-t), AUC(0-inf). The following secondary PK parameters will be summarized: AUC(0-24), t1/2, tmax, tlag, C24, and Ct. Additional PK parameters may also be summarized: e.g., Vz/F, and CL/F.

Endpoint	Statistical Analysis Methods
Primary	
Cohort 1	• The primary endpoints of this study are PK-related. The analysis for the primary PK endpoints will be performed for the PK Parameter Population. Plasma concentrations of DTG, ABC, and 3TC will be subjected to PK analyses using noncompartmental methods. • Based on the individual concentration-time data the following primary plasma PK parameters will be estimated: • AUC(0-inf), AUC(0-t) and Cmax

Endpoint	Statistical Analysis Methods
	• Analysis will be performed to compare the effect of food (high-fat meal) on the PK of DTG, ABC, and 3TC following administration of TRIUMEQ dispersible tablets compared to the PK of DTG, ABC, and 3TC following administration of TRIUMEQ dispersible tablets under fasted conditions. Analyses will be performed on the natural logarithms of AUC(0-inf), AUC(0-t), and Cmax using linear mixed effect models with treatment, sequence, and period as fixed effects and subject nested within sequence as a random effect. Effects will be estimated, and confidence intervals (CIs) will be constructed for the following treatment comparison: • Treatment A (test) versus Treatment B (reference) Point estimates and 90% CIs for treatment differences on the log scale derived from the model will be exponentiated to obtain estimates for geometric mean ratios and CIs on the original scale. • Summary statistics (arithmetic mean, geometric mean, median, standard deviation, minimum, maximum, and coefficient of variation) for plasma DTG, ABC, and 3TC primary PK parameter values will be summarized by treatment.
Cohort 2	• The primary endpoints of this study are PK-related. The analysis for the primary PK endpoints will be performed for the PK Parameter Population. Plasma concentrations of DTG and 3TC will be subjected to PK analyses using noncompartmental methods. • Based on the individual concentration-time data the following primary plasma PK parameters will be estimated: • AUC(0-inf), AUC(0-t) and Cmax • Analysis will be performed to compare the effect of food (high-fat meal) on the PK of DTG and 3TC following administration of DOVATO dispersible tablets compared to the PK of DTG and 3TC following administration of DOVATO dispersible tablets under fasted conditions. Analyses will be performed on the natural logarithms of AUC(0-inf), AUC(0-t), and Cmax using linear mixed effect models with treatment, sequence, and period as fixed effects and subject nested within sequence as a random effect. Effects will be estimated, and confidence intervals (CIs) will be constructed for the following treatment comparison: • Treatment C (test) versus Treatment D (reference) Point estimates and 90% CIs for treatment differences on the log scale derived from the model will be exponentiated to obtain estimates for geometric mean ratios and CIs on the original scale. • Summary statistics (arithmetic mean, geometric mean, median, standard deviation, minimum, maximum, and coefficient of variation) for plasma DTG and 3TC primary PK parameter values will be summarized by treatment.

Endpoint	Statistical Analysis Methods
Secondary Cohort 1 and Cohort 2	• Based on the individual concentration-actual time data the following secondary plasma PK parameters will be estimated: • tmax, tlag, t1/2, AUC(0-24), Ct, and C24 • Summary statistics (arithmetic mean, geometric mean, median, standard deviation, minimum, maximum, and coefficient of variation) for plasma DTG, ABC, and 3TC secondary PK parameter values will be summarized by treatment. • Summary statistics (arithmetic mean, median, standard deviation, minimum, maximum, and coefficient of variation) for plasma DTG, ABC, and 3TC PK concentrations will be summarized by treatment using the PK Concentration Population.

9.4.2. Safety Analysis

All safety analyses will be performed on the Safety Population.

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

The details of the statistical analyses of safety data will be provided in the reporting and analysis plan (RAP).

9.4.3. Other Analysis

Palatability questionnaire variables will be summarized descriptively. Further details will be provided in the RAP.

Additionally, special statistical and data analysis considerations may be warranted in the event that COVID-19 or related epidemics or natural disasters may affect the study and data integrity. To the extent possible, these will be described in the main study RAP; alternatively, a separate RAP focusing on modified data handling rules (e.g., changes to analysis populations, visit windows, and endpoints) and analyses (e.g., sensitivity analyses to assess impact of and account for missing data) may be prepared, taking into account applicable regulatory guidance and industry best practices for handling such situations [DHHS, 2020; EMA, 2020].

9.5. Interim Analysis

No interim analysis is planned.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. 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 International Ethical Guidelines.
    - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
    - Applicable laws and regulations.
- The protocol, protocol amendments, ICF, CIB, 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.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation 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/IEC.
    - Notifying the IRB/IEC of SAEs 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), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient and 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.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his or her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or his or her 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 requirements, where applicable, and the IRB/IEC or study center.
- 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 his or her legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

VH/GSK (alone or working with others) may use participant's coded study data and samples and other information to carry out this study; understand the results of this study; learn more about TRIUMEQ and DOVATO or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have the TRIUMEQ and DOVATO approved for medical use or approved for payment coverage.

The ICF may contain a separate section that addresses the use of participant data and remaining samples for optional further research. The investigator or authorized designee will inform each participant of the possibility of further research not related to the study/disease. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any participant data and/or remaining leftover samples to be used for further research not related to the study/disease. Participants who decline further research will tick the corresponding "No" box.

10.1.4. 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 or 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 who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his or 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.

10.1.5. Committees Structure

Not applicable.

10.1.6. 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 VH/GSK site or other mutually-agreeable location.
- VH/GSK will also provide all investigator who participated in the study with a summary of the study results . The investigator is encouraged to share the summary results with the study participant, 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 VH/GSK Policy.
- VH/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.
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRFs 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 eCRF.
- Guidance on completion of eCRFs will be provided in the eCRF Completion Guidelines.
- Quality tolerance limits (QTL) will be predefined in the QTL report to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during and at the end of the study and

all deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.

- 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 including definition of study critical data items and processes (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. Detailed information about study data collection and management process including systems used can be found in the study data management plan.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICFs, 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/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.

10.1.8. 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 and its origin can be found in SRM.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF 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.

10.1.9. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first participant screened and will be the study start date.

Study/Site Termination

VH/GSK or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of VH/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:

For study termination:

- Discontinuation of further study intervention development.

For site termination:

- 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 or no recruitment of participants (evaluated after a reasonable amount of time) by the investigator.
- If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate participant therapy and/or follow-up.

10.1.10. 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 multicenter 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.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 1 will be performed by the local laboratory.
- 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.

Table 1 Protocol-Required Safety Laboratory Tests

Laboratory Assessments	Parameters		
Hematology	Platelet count Red blood cell count Hemoglobin Hematocrit	Red blood cell indices: Mean corpuscular volume Mean corpuscular hemoglobin	White blood cell count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils Absolute neutrophil count
Clinical Chemistry[1]	Blood urea nitrogen	Calcium	Total and direct bilirubin
	Creatinine	AST	Total protein
	Glucose (fasting)	ALT	Albumin
	Potassium	Alkaline phosphatase[2]	Creatine phosphokinase
	Sodium		
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, and ketones by dipstick • Microscopic examination (if blood or protein is abnormal)		
Pregnancy testing	• Highly sensitive human chorionic gonadotropin pregnancy test (as needed for women of childbearing potential)[3]		
Other Screening Tests	• Follicle Stimulating Hormone and estradiol (as needed in women of non-childbearing potential only) • Alcohol, cotinine, and drug screen (to include at minimum: amphetamines, barbiturates, cannabinoids, cocaine or phencyclidine, or nonprescribed opiates, oxycodone, benzodiazepines, methadone, or tricyclic antidepressants) • Serology: HIV-1 and -2 antigen/antibody immunoassay, hepatitis B surface antigen, and hepatitis C antibody • *HLA-B*5701* screening • Creatine clearance for GFR estimation		

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 5. All events of ALT ≥3 × ULN and total bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and INR >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported to VH/GSK in an expedited manner (excluding studies of hepatic impairment or cirrhosis).

2. If alkaline phosphatase is elevated, consider fractionating .A new 5 mL SST blood sample will need to be drawn.
3. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

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

10.3.1. 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 Meeting 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 intervention- intervention 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 NOT 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 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.

10.3.2. Definition of SAE

An SAE is defined as any serious adverse event that, at any dose:
a. Results in death
b. 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.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted (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.
d. Results in persistent or significant 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 (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Possible Hy's Law case: ALT≥3 × ULN AND total bilirubin ≥2 × ULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5 must be reported as a SAE. • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that 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 for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. 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 (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to VH/GSK in lieu of completion of the VH/GSK required form. • There may be instances when copies of medical records for certain cases are requested by VH/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 VH/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 study should be evaluated by the investigator and graded in the eCRF according to the Division of Acquired Immune Deficiency Syndrome (DAIDS) grading table Version 2.1, July 2017 (https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf)

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 1 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 causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

  Note: An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

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 CIB 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 or 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 VH/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 VH/GSK.**
- The investigator may change his or 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 VH/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 VH/GSK with a copy of any postmortem findings including histopathology. • New or updated information will be recorded in the originally submitted documents. • The investigator will submit any updated SAE data to VH/GSK within 24 hours of receipt of the information.

10.3.4. Reporting of Serious Adverse Events to VH/GSK

SAE Reporting to VH/GSK via Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to VH/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) 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 study intervention/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 VH/GSK medical monitor by telephone. • Contacts for SAE reporting can be found in the SRM.

SAE Reporting to VH/GSK via Paper Data Collection Tool
• Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the VH/GSK medical monitor.

- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in the SRM.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions:

Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming postmenopausal unless permanently sterile (see below)

Notes:

- 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). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement (>40 IU/L or mIU/mL) is required.
    - 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.
- Permanent sterilization methods (for the purpose of this study) include:
    - 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, gonadal dysgenesis), 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.
-

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.

10.4.2. Contraception Guidance:

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[b] That Have Low User Dependency** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device
• Intrauterine hormone-releasing system[c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) • Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
• **Highly Effective Methods[b] That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  • oral
  • intravaginal
  • transdermal
  • injectable

• Progestogen-only hormone contraception associated with inhibition of ovulationc
  • oral
  • injectable

• Sexual abstinence • *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant*
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

c. Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, symptothermal, post ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction).

10.5. Appendix 5: Liver Safety: Required Actions and Follow-up Assessments

Table 2 Phase 1 Liver Chemistry Stopping Criteria and Required Follow-Up Assessments

Phase 1 Liver chemistry stopping criteria have been designed to assure subject safety and to evaluate liver event etiology

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT≥3 × ULN
If ALT≥3 × ULN AND total bilirubin≥ 2 × ULN (>35% direct bilirubin) or INR >1.5, report to VH/GSK as an SAE[1,2].
See additional Actions and Follow-Up Assessments listed below.</td></tr>
<tr><th colspan="3">Required Actions, Monitoring and Follow-Up Assessments</th></tr>
<tr><th colspan="2">Actions</th><th>Follow-Up Assessments</th></tr>
<tr><td colspan="2">• Report the event to VH/GSK within 24 hours
• Complete the liver event form 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 ≥3 × ULN AND total bilirubin ≥2 × ULN or INR >1.5
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin, and INR) and perform liver event follow-up assessments within 24 hours
• Monitor participant twice weekly until liver chemistries resolve, stabilise or return to within baseline
• A specialist or hepatology consultation is recommended
If ALT≥3 × ULN AND total bilirubin <2 × ULN and INR ≤1.5:
• Perform liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin, and INR) and perform liver event follow-up assessments within 24-72 hours
• Monitor participant weekly until liver chemistries</td><td>• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the aminotransferase values show downward trend
• Obtain serum creatine phosphokinase and lactate dehydrogenase
• Fractionate bilirubin, if total bilirubin≥2 × ULN
• 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 event form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, and other over-the-counter medications.
• Record alcohol use on the liver event alcohol intake in the eCRF
If ALT≥3 × ULN AND total bilirubin ≥2 × ULN or INR >1.5 obtain the following in addition to the assessments listed above:
• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G or gamma globulins.
• Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to</td></tr>
</table>

Liver Chemistry Stopping Criteria	
resolve, stabilize, or return to within baseline	evaluate liver disease; complete liver imaging and/or liver biopsy CRF.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation testing is not immediately available, discontinue study intervention for that participant if ALT ≥3 x ULN and bilirubin 2 × ULN. 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 ≥3 × ULN and total bilirubin ≥ 2 × ULN (>35% direct bilirubin) or ALT ≥ 3 × ULN and INR >1.5, which may indicate severe liver injury (possible 'Hy's Law'), must be reported to VH/GSK as an SAE (excluding studies of hepatic impairment or cirrhosis); the INR threshold value stated will not apply to participants receiving anticoagulants.
3. Includes: hepatitis A immunoglobulin (IgM) antibody; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing) and hepatitis E IgM antibody.

10.6. Appendix 6: Clinical Protocol COVID-19: Recommended Measures Pandemic and Clinical Trial Continuity

COVID-19 pandemic may impact the conduct of clinical studies. Challenges may arise from quarantines, site closures, travel limitations, interruptions to the supply chain for the investigational product or other considerations if site personnel or study participants become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures, including administering or using the investigational product or adhering to protocol-mandated visits and laboratory/diagnostic testing.

Based on these challenges, it may be necessary to adopt additional measures and procedures to protect participant safety, and to ensure that there are no gaps in study treatment for participants enrolled in this clinical study.

In order to maintain the scientific integrity of the study and adhere to updated guidance from regulators, procedures have also been put into place to ensure that the actions taken to mitigate against any impact of COVID-19 are well documented in the trial database.

This appendix outlines measures that may be applicable for any site impacted by the COVID-19 pandemic. The purpose of the appendix is to provide information on the measures to be taken to protect participants' safety, welfare and rights, and promote data integrity.

These measures will remain in place until the site is able to resume normal working activities OR until study completion/other time period.

10.6.1. Study Procedures During COVID-19 Pandemic

During the special circumstances caused by the current COVID-19 pandemic, you should consider specific public health guidance, the impact of any travel restrictions implemented by local/regional health authorities and local institutions, and individual benefit/risk when making enrollment and treatment decisions for trial participants.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow-up; however when not possible, for the duration of these special circumstances, the following measures may be implemented for enrolled participants.

- Investigators should document in site files and in participant source documents how restrictions related to COVID-19 led to the changes in study conduct and duration of those changes and indicate which study participants were impacted and how those trial participants were impacted (as per the current local COVID-19 related regulatory guidance).
- Missing protocol-required data/visits due to COVID-19 should be noted in participant notes and recorded as a COVID-19 protocol deviation.

10.7. Appendix 7: Toxicity Management

Adverse events that occur during the trial should be evaluated by the investigator and graded according to the DAIDS toxicity scales (see Appendix 8). Additional information regarding detecting, documenting and reporting AEs and SAEs are available in Appendix 3.

Study drug may be stopped at the discretion of the investigator and according to the severity of the AE.

No toxicity-related dose reductions of study drugs will be allowed. Guidance is provided below on participant management. All changes in study intervention must be accurately recorded in the participant's eCRF.

NOTE: In the event of a discontinuation of DTG/ABC/3TC FDC for any reason, the investigator must obtain a complete history of the events surrounding the discontinuation of DTG/ABC/3TC FDC, evaluate for the possibility of a clinically suspected hypersensitivity reaction, and initiate participant management as outlined in the DTG CIB, regardless of a subject's *HLA-B*5701* status.

Grade 1 or Grade 2 Toxicity/Adverse Event

Participants who develop a Grade 1 or Grade 2 AE or toxicity may continue study intervention at the discretion of the investigator. Participants who choose to withdraw from the study due to a Grade 1 or 2 AE should have study withdrawal and follow-up evaluations completed.

Grade 3 Toxicity/Adverse Event

Participants who develop a Grade 3 AE or toxicity should be managed as follows:

If the investigator has compelling evidence that the Grade 3 AE or toxicity has not been caused by study intervention, dosing may continue after discussion with the medical monitor.

Participants who develop a Grade 3 AE or toxicity that the investigator considers related or possibly related to the study intervention should have study intervention permanently discontinued.

Participants with asymptomatic Grade 3 laboratory abnormalities require permanent discontinuation and study drug and should be investigated for all potential non-drug related causes.

Exceptions are noted for rash and hypersensitivity reactions in Section 10.7.1.3.

Grade 4 Toxicity/Adverse Event

Participants who develop a Grade 4 AE or toxicity should have study intervention discontinued.

Participants experiencing Grade 4 AEs requiring permanent discontinuation of study intervention should be followed weekly until resolution of the AE and encouraged to complete the withdrawal and follow-up study evaluations as noted above.

Participants with asymptomatic Grade 4 laboratory abnormalities require permanent discontinuation of study drug and should be investigated for all potential non-drug related causes. An in-clinic follow-up visit will be conducted approximately 4 weeks after the last dose of study medication for subjects with ongoing AEs and SAEs and also any laboratory abnormalities that are considered to be AEs or potentially harmful to the subject, at the last on-study visit.

10.7.1. Specific Toxicities/Adverse Event Management

General guidelines for the management of specific toxicities that are considered to be related or possibly related to study treatment are provided below.

Participants who permanently discontinue study intervention for reasons of toxicity should be followed weekly until resolution of the AE and encouraged to complete the withdrawal and follow-up study evaluations (Section 8.3.3).

10.7.1.1. Liver Chemistry Stopping and Follow-up Criteria

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event aetiology during administration of study drug and the follow-up period. For a complete listing of stopping and follow-up criteria refer to Appendix 5.

10.7.1.2. Decline in Renal Function

Participants who experience an increase in serum creatinine from baseline of 45 micromoles/liter (μMol/L) (or 0.5 milligrams/deciliter [mg/dL]) should return for a confirmatory assessment within 2 to 4 weeks. A urinalysis and urine albumin/creatinine and urine protein/creatinine ratios, serum cystatin C, and an estimated GFR using the CKD-EPI cystatin C method [Inker, 2012] should also be done at this confirmatory visit (refer to the SRM for details on the collection and processing of these urine samples). If the creatinine increase is confirmed, the investigator should contact the study medical monitor to discuss additional follow-up and medical management.

10.7.1.3. Hypersensitivity reaction

Both ABC and DTG are associated with a risk for hypersensitivity reactions and share some common features such as fever and/or rash with other symptoms indicating multiorgan involvement. Clinically it is not possible to determine whether a hypersensitivity reaction with DTG/ABC/3TC FDC is caused by ABC or DTG. Hypersensitivity reactions have been observed more commonly with ABC, some of which have been life-threatening, and in rare cases fatal, when not managed appropriately. More detailed clinical descriptions of these reactions are included in the DTG/ABC/3TC CIB [GSK Document Number RM2007/00683/14].

The risk for ABC hypersensitivity reactions to occur is significantly increased for patients who test positive for the *HLA-B*5701* allele. However, ABC hypersensitivity reactions have been reported at a lower frequency in patients who do not carry this allele. In the prospective study CNA106030 (PREDICT-1), the use of pre-therapy screening for the presence of *HLA-B*5701* and subsequently avoiding ABC in *HLA-B*5701* positive patients, significantly reduced the incidence of clinically suspected ABC hypersensitivity reactions from 7.8% (66 of 847) to 3.4% (27 of 803) ($p<0.0001$) [Mallal, 2008]. In clinical studies EPZ108859 (ARIES) and CNA109586 (ASSERT), 0.8% (4/515) and 3.1% (6/192) of subjects who were *HLA-B*5701* negative and who received ABC developed a clinically suspected ABC hypersensitivity reaction, respectively [Post, 2010; Squires, 2010].

With reference to the DTG/ABC/3TC CIB and the 'Subject Information and Consent Form', investigators must ensure that participants are fully informed regarding the risk of hypersensitivity reactions prior to commencing ABC therapy. Each participant should also be reminded of the importance of reading the Alert Card accompanying their study medication and keeping it with them at all times.

The following should be adhered to in the management of participants presenting with signs and symptoms suggesting a possible hypersensitivity reaction:

- In any participant treated with DTG/ABC/3TC, the clinical diagnosis of suspected hypersensitivity reaction must remain the basis of clinical decision making.
- **DTG/ABC/3TC must be stopped without delay, even in the absence of the HLA-B*5701 allele, if a hypersensitivity reaction is suspected. Delay in stopping treatment with after the onset of hypersensitivity may result in a life-threatening reaction.** Clinical status including liver aminotransferases and bilirubin should be monitored.
- Subjects who have experienced a hypersensitivity reaction should not restart ABC.
- **After stopping treatment with DTG/ABC/3TC for reasons of a suspected hypersensitivity reaction, DTG/ABC/3TC or any other medicinal product containing ABC or DTG must never be reinitiated.**
- **Restarting ABC-containing products following a suspected ABC hypersensitivity reaction can result in a prompt return of symptoms within hours and may include life-threatening hypotension and death.**

10.7.1.3.1. Reporting of Hypersensitivity Reactions

If a clinically suspected case of hypersensitivity reaction to ABC meets one of the ICH-E2A definitions of seriousness listed in Appendix 3 then, in addition to reporting the case as an SAE, the ABC hypersensitivity reactions printed or eCRF should also be completed within one week of the onset of the hypersensitivity reaction.

10.7.1.4. Skin Reactions without Other Symptoms that are Typical of Abacavir Hypersensitivity Reactions

Including serious skin reactions such as Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, Erythema Multiforme or rash with significant liver dysfunction

Participants should be instructed to contact the investigator as soon as possible if they develop a rash while on study.

Subjects who develop rash of any grade should be evaluated for the possibility of an ABC hypersensitivity reaction or a serious skin reaction such as Stevens-Johnson syndrome, toxic epidermal necrolysis, or erythema multiforme. Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme have been reported very rarely in patients taking ABC-containing products. These patients generally do not have the cluster of additional symptoms (e.g., gastrointestinal and respiratory) that characterize the ABC hypersensitivity reaction, but they do have features typical of these serious skin reactions.

If a serious skin reaction develops, ABC should be discontinued, and the subject should not be re-challenged with any ABC-containing medicinal product (i.e., TRIUMEQ, ZIAGEN™, TRIZIVIR™, EPZICOM, or KIVEXA).

Mild to moderate rash is an expected adverse reaction for DTG-containing ART. Episodes generally occur within the first 10 weeks of treatment, rarely require interruptions or discontinuations of therapy and tend to resolve within 2 to 3 weeks. The index case of hypersensitivity with DTG involved a profuse, purpuric, and coalescing leukocytoclastic vasculitis as well as clinically significant liver chemistry elevations. Other than this case, no other instances of serious skin reaction, including Stevens-Johnson Syndrome, toxic epidermal necrolysis, and erythema multiforme, have been reported for DTG in clinical trials.

The following guidance is provided for clinical management of participants who experience rash alone in the absence of accompanying diagnosis of ABC hypersensitivity reaction, systemic or allergic symptoms or signs of mucosal, or target lesions.

Participants with an isolated Grade 1 rash may take the second dose of study drug at the investigator's discretion. 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 involvement develops.

Participants may take the second dose of study drug for an isolated Grade 2 rash. However, study drug should be permanently discontinued for any Grade ≥2 rash that is associated with an increase in ALT (Section 7.1.1). The participant should be advised to contact the physician immediately if a rash fails to resolve (after more than 2 weeks), if there is any worsening of the rash, if any systemic signs or allergic symptoms develop, or if mucosal involvement develops.

Participants should permanently discontinue study drug for an isolated Grade 3 or 4 rash, and the participant should be withdrawn from the study. Participants should be treated as clinically appropriate and followed until resolution of the AE.

The rash and any associated symptoms should be reported as AEs (Section 8.3) and appropriate toxicity ratings should be used to grade the events (based on DAIDS toxicity gradings).

If the etiology of the rash can be definitely diagnosed as being unrelated to the study intervention and due to a specific medical event or a concomitant

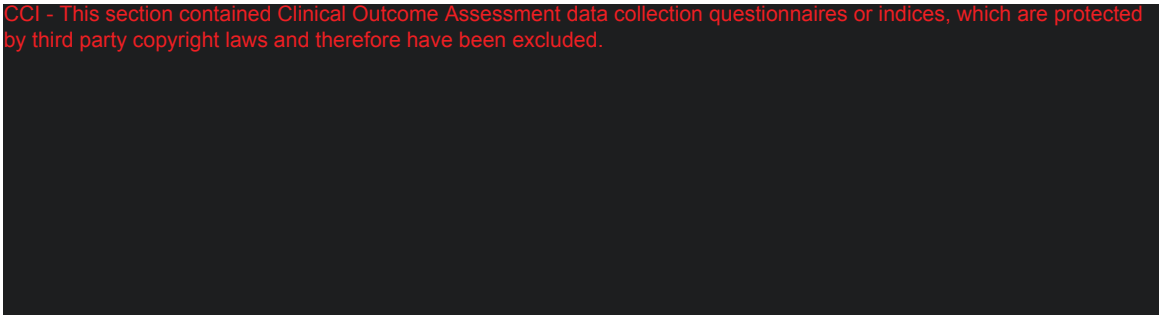
10.7.1.5. Creatine Phosphokinase Elevation

A Grade 3 or higher elevation in CPK should result in a repeat assessment within 2 to 4 weeks to ensure the result is transient or due to exercise and will not require a change in study intervention. A history regarding use of drugs known to cause increase of CPK (such as statins), physical activity, or exercise preceding the CPK evaluation should be obtained. Grade 4 elevations in CPK should have a repeat assessment after the participant has abstained from exercise for >24 hours.

10.8. Appendix 8: Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Corrected Version 2.1, July 2017

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events is a descriptive terminology which can be utilized for AE reporting. A grading (severity) scale is provided for each AE term [DHHS, 2017] (https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf).

Estimating Severity Grade for Parameters Not Identified in the Grading Table
The functional table 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.



10.9. Appendix 9: Abbreviations and Trademarks

3TC	Lamivudine
ABC	Abacavir
AE	Adverse event
AIDS	Acquired immune deficiency syndrome
ALT	Alanine transaminase
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC(0-24)	Area under the plasma concentration-time curve from time zero to twenty-four hours
AUC(0-inf)	Area under the plasma concentration-time curve from time zero extrapolated to infinity
AUC(0-t)	Area under the concentration-time curve from time zero to time of last observed quantifiable concentration
C24	Concentration at twenty-four hours post-dose
CI	Confidence interval
CIB	Clinical Investigator Brochure
CL/F	Apparent oral clearance
Cmax	Maximum observed plasma concentration
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CRF	Case report form
CVw%	Within participant variability
DAIDS	Division of AIDS
DHHS	Department of Health and Human Services
DTG	Dolutegravir
ECG	Electrocardiogram
eCRF	Electronic case report form
EU	European Union
FDA	Food and Drug Administration
FDC	Fixed-dose combination
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GSK	GlaxoSmithKline
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HRT	Hormone replacement therapy
ICF	Informed consent form
IEC	Independent Ethics Committee

INI	Integrase inhibitor
INR	International normalized ratio
IRB	Institutional Review Board
PK	Pharmacokinetic(s)
QTc	Corrected QT interval
QTcF	Corrected QT interval according to Fridericia's formula
QTL	Quality tolerance limit
RAP	Reporting and analysis plan
RNA	Ribonucleic Acid
SAE	Serious adverse event
SoA	Schedule of Activities
SRM	Study reference manual
SUSAR	Serious Unexpected Serious Adverse Reactions
t1/2	Terminal elimination phase half-life
tlag	Lag time for absorption
Tmax	Time to maximum observed concentration taken directly from the concentration-time profile
ULN	Upper limit of normal
US	United States
VH	ViiV Healthcare
Vz/F	Apparent volume of distribution
WOCBP	Women of child bearing potential

Trademark Information

Trademarks of the ViiV Healthcare and GlaxoSmithKline group of companies
DOVATO
KIVEXA/EPZICOM
TIVICAY
TRIUMEQ
TRIZIVIR
ZIAGEN

Trademarks not owned by the ViiV Healthcare and GlaxoSmithKline group of companies
WinNonlin

11. REFERENCES

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Drug Evaluation and Research, Center for Drug Evaluation and Research (US). Guidance for Industry: Food-effect bioavailability and fed bioequivalence studies. December 2002. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/food-effect-bioavailability-and-fed-bioequivalence-studies

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research (US). Guidance for Industry, Investigators, and Institutional Review Boards. Conduct of clinical trials of medical products during the COVID-19 public health emergency. December 2020. Available from: https://www.fda.gov/regulatoryinformation/search-fda-https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-public-health-emergency

Department of Health and Human Services (DHHS), 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 pediatric adverse events, Corrected Version 2.1. July 2017. Available from: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

DOVATO Prescribing Information (dolutegravir, and lamivudine tablets), for oral use. August, 2019.

European Medicines Agency (EMA). Science Medicines Health, Committee for Human Medicinal Products. Points to consider on implications of coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials. June 2020. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/points-consider-implications-coronavirus-disease-covid-19-methodological-aspects-ongoing-clinical_en-0.pdf.

GlaxoSmithKline Document Number 2017N330422_00. Study 205894A 2-Part, Phase I, Single-Dose, 3-Period Crossover Relative Bioavailability Study of a Pediatric TRIUMEQ Dispersible Tablet and Pediatric Dolutegravir and Lamivudine (DTG/3TC) Fixed Dose Combination Dispersible Tablet Formulations as Compared With Adult Tablets in Healthy Volunteers. 2018.

GlaxoSmithKline Document Number RM2007/00683/14: GSK1349572 Clinical Investigator's Brochure, version 14. September 2020.

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.

Mallal S, Phillips E, Carosi G, Molina JM, Workman C, Tomazic J, et al. HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med. 2008;358(6):568-79.

Post FA, Moyle GJ, Stellbrink HJ, Domingo P, Podzamczer D, Fisher M, et al. Randomized comparison of renal effects, efficacy, and safety with once-daily abacavir/lamivudine versus tenofovir/emtricitabine, administered with efavirenz, in antiretroviral-naive, HIV-1-infected adults: 48-week results from the ASSERT study. J Acquir Immune Defic Syndr. 2010;55(1):49-57.

Squires KE, Young B, DeJesus E, Bellos N, Murphy D, Sutherland-Phillips DH, et al. Safety and efficacy of a 36-week induction regimen of abacavir/lamivudine and ritonavir-boosted atazanavir in HIV-infected patients. HIV Clin Trials. 2010;11(2):69-79.

TIVICAY Prescribing Information (dolutegravir), or oral use. August 2013.

TRIUMEQ Prescribing Information (abacavir, dolutegravir, and lamivudine tablets), for oral use. August, 2014.