TITLE PAGE

Protocol Title: A 2-Part, Phase I, Single-Dose, 3-Period Crossover Relative Bioavailability Study of a Pediatric TRIUMEQ Dispersible Tablet and Pediatric Dolutegravir and Lamivudine (DTG/3TC) Fixed Dose Combination Dispersible Tablet Formulations as Compared With Adult Tablets in Healthy Volunteers

Protocol Number: 205894

Short Title: Relative Bioavailability of TRIUMEQ and DTG/3TC Pediatric Dispersible Tablet Formulations in Healthy Volunteers

Compound Numbers: GSK2619619 (GSK1349572+GR109714+GI265235) and GSK3515864 (GSK1349572+GR109714)

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1. SYNOPSIS

Protocol Title: A 2-Part, Phase I, Single-Dose, 3-Period Crossover Relative Bioavailability Study of a Pediatric TRIUMEQ Dispersible Tablet and Pediatric Dolutegravir and Lamivudine (DTG/3TC) Fixed Dose Combination Dispersible Tablet Formulations as Compared With Adult Tablets in Healthy Volunteers

Short Title: Relative Bioavailability of TRIUMEQ and DTG/3TC Pediatric Dispersible Tablet Formulations in Healthy Volunteers

Rationale:

This study will compare the relative bioavailability (BA) of TRIUMEQ dispersible tablets developed for pediatric populations (dolutegravir [DTG] 5 mg/abacavir [ABC] 60 mg/lamivudine [3TC] 30 mg), when administered as direct-to-mouth and when dispersed into purified water, with the adult TRIUMEQ conventional tablet (DTG 50 mg/ABC 600 mg/3TC 300 mg) when administered as direct-to-mouth (reference). In addition, this study will compare the relative BA of DTG/3TC (DTG 5 mg/3TC 30 mg) dispersible tablets developed for pediatric populations, when administered as direct-to-mouth and when dispersed into purified water, with the adult DTG (50 mg) and 3TC (300 mg) conventional tablets when administered as direct-to-mouth (reference).

Objectives and Endpoints:

Objectives	Endpoints
Part 1	
Primary	
• To compare the relative BA of DTG, ABC, and 3TC administered as pediatric TRIUMEQ dispersible tablets with the conventional adult TRIUMEQ tablet (reference) administered as direct-to-mouth when: o Pediatric TRIUMEQ dispersible tablets are administered as a dispersion and taken immediately o Pediatric TRIUMEQ dispersible tablets are administered as direct-to-mouth	• Plasma DTG, ABC, and 3TC: o Area under the plasma concentration-time curve (AUC) from time of dose extrapolated to infinity (AUC[0-∞]) o AUC from time of dose to last measurable concentration (AUC[0-t]) o Maximum observed concentration (Cmax)
Secondary	
• To compare the single-dose pharmacokinetics (PK) of DTG, ABC, and 3TC administered as pediatric TRIUMEQ dispersible tablets with the conventional adult TRIUMEQ tablets (reference) administered as direct-to-mouth when: o Pediatric TRIUMEQ dispersible tablets are administered as a dispersion and taken immediately o Pediatric TRIUMEQ dispersible tablets are administered as direct-to-mouth	• Plasma DTG, ABC, and 3TC: o AUC from time of dose to 24 hours (AUC[0-24]) o Time to maximum concentration (Tmax) o Time of last quantifiable concentration (Tlast) o Apparent oral clearance (CL/F) o Apparent volume of distribution (Vz/F) o Observed concentration at 24 hours postdose (C24) o Last observed quantifiable concentration (Ct) o Terminal elimination phase half-life (t½) • Plasma DTG: o Lag time for absorption (tlag)
• To evaluate the safety and tolerability of DTG, ABC, and 3TC administered as pediatric TRIUMEQ dispersible tablets as compared with conventional adult TRIUMEQ tablet (reference) administered as direct-to-mouth	• Safety and tolerability parameters for adverse events (AE)/serious adverse events (SAE), observed and change from baseline clinical laboratory assessments, electrocardiogram (ECG), and vital signs

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

Overall Design:

This is a 2-part, open-label, single-dose, 3-period, randomized, crossover study to compare the relative BA of pediatric TRIUMEQ dispersible tablets with an adult TRIUMEQ conventional tablet formulation (Part 1) and of pediatric DTG/3TC dispersible tablets with adult DTG and 3TC conventional tablets formulation (Part 2) in healthy volunteers under fasted conditions. Prior to dosing on Day 1 of Period 1 in each part, participants will be randomized to 1 of 6 treatment sequences (ABC, BCA, CAB, ACB, BAC, or CBA in Part 1; DEF, EFD, FDE, DFE, EDF, or FED in Part 2) and will receive a single dose of each of the 3 treatments administered as 1 treatment per period.

Parts 1 and 2 of the study are independent of one another and may be run in parallel. Study assessments will be performed as indicated in the Schedule of Activities.

Number of Participants:

For each part, sufficient participants will be screened to achieve 18 randomized, each to 1 of 6 treatment sequences, to achieve approximately 12 evaluable participants that have completed all 3 treatment periods (2 evaluable participants per sequence).

Treatment Groups and Duration:

In each part, participants will receive a single dose of each of the following treatments, administered as 1 treatment per period according to their assigned sequence:

Part 1:

- Treatment A: Adult TRIUMEQ (DTG 50 mg/ABC 600 mg/3TC 300 mg, 1 conventional tablet) administered as direct-to-mouth (reference).
- Treatment B: Pediatric TRIUMEQ (DTG 5 mg/ABC 60 mg/3TC 30 mg, 10 dispersible tablets) administered as a dispersion and taken immediately (test).
- Treatment C: Pediatric TRIUMEQ (DTG 5 mg/ABC 60 mg/3TC 30 mg, 10 dispersible tablets) administered as direct-to-mouth (test).

Part 2:

- Treatment D: Adult DTG (50 mg, 1 conventional tablet) and adult 3TC (300 mg, 1 conventional tablet) administered as direct-to-mouth (reference).
- Treatment E: Pediatric DTG/3TC (DTG 5 mg/3TC 30 mg, 10 dispersible tablets) administered as a dispersion and taken immediately (test).
- Treatment F: Pediatric DTG/3TC (DTG 5 mg/3TC 30 mg, 10 dispersible tablets) administered as direct-to-mouth (test).

To ensure adequate washout, there will be at least 7 days between each dose of study drug, 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. In each of the 3 treatment periods, participants will be admitted to the clinic on Day −1 and will be discharged

following completion of the last study procedure on Day 4. Participants will return to the clinic for an outpatient follow-up visit 7 to 10 days after the last dose of study drug.

The total duration of participation in this study will be approximately 9 weeks, including a screening visit within 30 days prior to the first dose of study drug, 3 treatment periods each with a single dose of study drug per treatment period, and a follow-up visit within 7 to 10 days after the last dose of study drug.

2. SCHEDULE OF ACTIVITIES (SOA)

2.1. Screening Assessments for Parts 1 and 2

- Screening procedures may be done over more than one visit but must all be completed within 30 days prior to the first dose of study drug.
- 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.

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

2.2. Time and Events Table for Parts 1 and 2

Assessments	Periods 1-3							Follow-up	Notes
	Day −1	Day 1			Day 2	Day 3	Day 4		
		Predose	0 hr	Postdose	24 hr	48 hr	72 hr		
Admission to Unit	X								
Discharge							X		
Outpatient Visit								X	*Follow-up visit will occur 7-10 days after last dose.*
12-lead ECG (single)	X								
Vital signs	X	X		At 4 hours postdose	X			X	• *Single vital sign measurements performed at all time points.* • *Vital signs at Follow-up are only necessary if participant had ongoing AEs or a previous abnormal vital sign result of clinical concern. Only the abnormal value(s) need be re-assessed.*
Brief Physical Examination	X								*Physical examination required only on Day −1 of Period 1 and as needed based on AE assessment.*
Urine Drug/Alcohol/Cotinine	X								• *Drug/Alcohol/Cotinine/pregnancy will be performed as per the standard practice of the site.* • *For clinical laboratory tests, see Appendix 2.* • *Clinical laboratory tests at Follow-up are only necessary if participant had ongoing AEs or a previous abnormal clinical laboratory result of clinical concern. Only the abnormal value(s) need be re-assessed.*
Pregnancy test (serum; WOCBP)	X							X	
Clinical laboratory tests	X				X			X	
Dosing			**X**						*Participants in Part 1 should be provided with an ABC HSR warning card and should be reminded to read it.*
Palatability Assessment				Start within 10 minutes after dose					*Complete for each dispersion treatment (Treatments B & E, see Appendix 4).*
Pharmacokinetic Sampling		X		Collect at: 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 16, 24, 48 and 72 hours postdose before discharge at the end of each period					*Predose is within 15 minutes prior to dosing (see Section 9.5.1).*
Meals	Fasted from 10 hours prior to dosing to 4 hours postdose			Standard for the study centre					
Adverse Events / SAE	X	←==========X==========→						X	
Concomitant medications	X	←==========X==========→						X	

- The timing and number of planned study assessments, including safety, pharmacokinetic 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 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 IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

3. INTRODUCTION

TRIUMEQ™ (GSK2619619) is a fixed-dose combination (FDC) that contains the integrase inhibitor (INI) dolutegravir (DTG [TIVICAY™, GSK1349572]) and 2 nucleoside reverse transcriptase inhibitors, abacavir (ABC) and lamivudine (3TC).

GSK3515864 is an FDC in development that contains the INI DTG (TIVICAY, GSK1349572) and the nucleoside reverse transcriptase inhibitor 3TC.

3.1. Study Rationale

An ABC/3TC conventional tablet is currently marketed worldwide for the treatment of human immunodeficiency virus (HIV) in adults and children (as EPZICOM™ in the United States [US] or as KIVEXA™ in the European Union [EU]). The TIVICAY 50 mg conventional tablet is for the treatment of HIV infection in adults and adolescents. Recently, 2 lower pediatric-strength conventional tablets (10 mg and 25 mg) were approved in the US and EU. A dispersible-tablet formulation (5-mg tablet for oral suspension) of TIVICAY has been developed for administration in younger pediatric populations.

This study will compare the relative bioavailability (BA) of TRIUMEQ dispersible tablets developed for pediatric populations (DTG 5 mg/ABC 60 mg/3TC 30 mg), when administered as direct-to-mouth and when dispersed into purified water, with the adult TRIUMEQ conventional tablet (DTG 50 mg/ABC 600 mg/3TC 300 mg) when administered as direct-to-mouth (reference). In addition, this study will compare the relative BA of DTG/3TC (DTG 5 mg/3TC 30 mg) dispersible tablets developed for pediatric populations, when administered as direct-to-mouth and when dispersed into purified water, with the adult DTG (50 mg) and 3TC (300 mg) conventional tablets when administered as direct-to-mouth (reference).

3.2. Background

TIVICAY, as a DTG single-drug entity, was first approved in the US in August 2013 and is currently approved globally in more than 100 countries. DTG is a next-generation INI with low to moderate inter-participant pharmacokinetic (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. In addition, DTG lacks many of the associated drug interactions, specifically with oral contraceptives, statins, antidepressants, anxiolytics, anticoagulants, and other medications commonly taken by HIV-positive patients.

The TRIUMEQ FDC tablet was developed and 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, or in combination with other antiretroviral therapies, to achieve convenient dosing and improve patient compliance. The TRIUMEQ conventional tablet (currently approved more than 50 countries) is bioequivalent to concurrent administration of DTG and ABC/3TC tablets (TRIUMEQ Prescribing Information, 2014). The DTG/3TC FDC tablet is currently being developed for treatment of HIV in adults. Alternate formulations

(e.g., dispersible tablets) and dosing strategies are being 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 DTG/3TC, is provided in the Investigator's Brochure (IB) [GlaxoSmithKline Document Number RM2007/00683/11].

3.3. 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 IB.

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy[1]
Investigational Product (IP) [DTG/ABC/3TC] Refer to IB for additional information on DTG and DTG/ABC/3TC Refer to approved country product label for additional information on DTG and ABC/3TC		
Hypersensitivity (including abacavir hypersensitivity reaction [ABC HSR]) and rash	A well characterized, idiosyncratic, drug-related HSR is the most important risk associated with ABC (Section 12.5.9). Exclusion of individuals found to carry the human leukocyte antigen (HLA)-B*5701 allele from ABC therapy reduces the risk of HSR. Rash, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and erythema multiforme have been reported in patients taking ABC (Section 12.5.1). HSR has been observed uncommonly with DTG. Rash was commonly reported in DTG Phase IIb/III clinical trials; episodes were generally mild to moderate in intensity; no episodes of severe rash, such as SJS, TEN, and erythema multiforme were reported. Data on HSR for DTG and DTG+ABC/3TC FDC suggest that there will not be additional risk from HSR in HLA-B*5701 negative participants receiving the DTG/ABC/3TC FDC.	• *Participants must be negative for HLA-B*5701 for inclusion in Part 1 (Section 6.1). Additionally, participants with history of allergy/sensitivity to any of the study drugs are excluded (Section 6.2).* • *Specific/detailed toxicity management guidance is provided for suspected HSR with DTG or ABC (Appendix 5), and skin reactions without systemic involvement (Appendix 5).* • *The participant informed consent form includes information on this risk and the actions participants should take in the event of an HSR or associated signs and symptoms.* • *Participants in Part 1 will be provided with an ABC HSR warning card and are to be reminded to read it.*
Drug induced liver injury (DILI) and other clinically significant liver chemistry elevations	Non-clinical data suggested a possible, albeit low, risk for hepatobiliary toxicity with DTG. Drug-related hepatitis is considered an uncommon risk for antiretroviral therapy (ART) containing DTG regardless of dose or treatment population. Current treatment guidelines [Guidelines 2016] 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 either of the following criteria during the screening period are excluded from participating (Section 6.2).* • *Alanine aminotransferase (ALT) ≥1.5 times the upper limit of normal (ULN; isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin ≤35%).* • *Positive for HBV (hepatitis B virus surface antigen positive [+HBsAg]) or positive HCV (positive hepatitis C antibody test) within 3 months of the Day 1 study visit.* *Specific/detailed liver chemistry stopping criteria (Section 8.1.1) 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 (OCT) 2 transporter, resulting in	*Concomitant medications (e.g., dofetilide) are prohibited in the study (Section 6.2 and Section 7.7).*

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy[1]
	potentially life-threatening toxicity.	
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 9.2 and Appendix 8).*
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 CrCl <90 mL/min are excluded (Section 6.2).* *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.*
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).*

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 9]). Serious/severe events will be managed appropriately including, but not limited to, withdrawal of investigational product (IP), and will be followed to resolution as per Sponsor's standard medical monitoring practices.

3.3.2. Benefit Assessment

This is a study in healthy participants and as such there is no expected benefit to administration of DTG, ABC, and 3TC. Participation in this study may contribute to the process of developing new therapies for 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.

3.3.3. Overall Benefit:Risk Conclusion

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with DTG, ABC, and 3TC are low.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Part 1	
Primary	
• To compare the relative BA of DTG, ABC, and 3TC administered as pediatric TRIUMEQ dispersible tablets with the conventional adult TRIUMEQ tablet (reference) administered as direct-to-mouth when: o Pediatric TRIUMEQ dispersible tablets are administered as a dispersion and taken immediately o Pediatric TRIUMEQ dispersible tablets are administered as direct-to-mouth	• Plasma DTG, ABC, and 3TC: o Area under the plasma concentration-time curve (AUC) from time of dose extrapolated to infinity (AUC[0-∞]) o AUC from time of dose to last measurable concentration (AUC[0-t]) o Maximum observed concentration (Cmax)
Secondary	
• To compare the single-dose pharmacokinetics (PK) of DTG, ABC, and 3TC administered as pediatric TRIUMEQ dispersible tablets with the conventional adult TRIUMEQ tablets (reference) administered as direct-to-mouth when: o Pediatric TRIUMEQ dispersible tablets are administered as a dispersion and taken immediately o Pediatric TRIUMEQ dispersible tablets are administered as direct-to-mouth	• Plasma DTG, ABC, and 3TC: o AUC from time of dose to 24 hours (AUC[0-24]) o Time to maximum concentration (Tmax) o Time of last quantifiable concentration (Tlast) o Apparent oral clearance (CL/F) o Apparent volume of distribution (Vz/F) o Observed concentration at 24 hours postdose (C24) o Last observed quantifiable concentration (Ct) o Terminal elimination phase half-life (t½) • Plasma DTG: o Lag time for absorption (tlag)
• To evaluate the safety and tolerability of DTG, ABC, and 3TC administered as pediatric TRIUMEQ dispersible tablets as compared with conventional adult TRIUMEQ tablet (reference) administered as direct-to-mouth	• Safety and tolerability parameters for adverse events (AE)/serious adverse events (SAE), observed and change from baseline clinical laboratory assessments, electrocardiogram (ECG), and vital signs

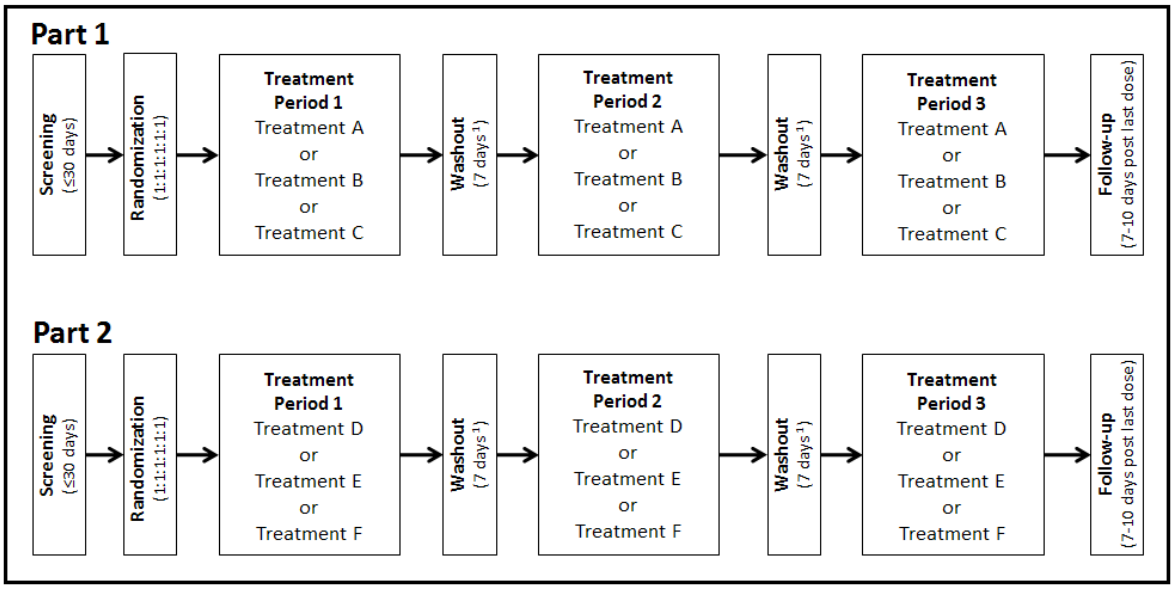
Objectives	Endpoints
Part 2	
Primary	
• To compare the relative BA of DTG and 3TC administered as pediatric DTG/3TC dispersible tablets with the conventional adult DTG and 3TC tablets (reference) administered as direct-to-mouth when: ○ Pediatric DTG/3TC dispersible tablets are administered as a dispersion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

5. STUDY DESIGN

5.1. Overall Design

This is a 2-part, open-label, single-dose, 3-period, randomized, crossover study to compare the relative BA of pediatric TRIUMEQ dispersible tablets with an adult TRIUMEQ conventional tablet formulation (Part 1) and of pediatric DTG/3TC dispersible tablets with adult DTG and 3TC conventional tablets formulation (Part 2) in healthy volunteers under fasted conditions. A study design schematic is presented in Figure 1.

Figure 1 Study Design Schematic



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

Prior to dosing on Day 1 of Period 1 in each part, participants will be randomized to 1 of 6 treatment sequences (ABC, BCA, CAB, ACB, BAC, or CBA in Part 1; DEF, EFD, FDE, DFE, EDF, or FED in Part 2) and will receive a single dose of each of the following treatments administered as 1 treatment per period:

Part 1:

- Treatment A: Adult TRIUMEQ (DTG 50 mg/ABC 600 mg/3TC 300 mg, 1 conventional tablet) administered as direct-to-mouth (reference).
- Treatment B: Pediatric TRIUMEQ (DTG 5 mg/ABC 60 mg/3TC 30 mg, 10 dispersible tablets) administered as a dispersion and taken immediately (test).
- Treatment C: Pediatric TRIUMEQ (DTG 5 mg/ABC 60 mg/3TC 30 mg, 10 dispersible tablets) administered as direct-to-mouth (test).

Part 2:

- Treatment D: Adult DTG (50 mg, 1 conventional tablet) and adult 3TC (300 mg, 1 conventional tablet) administered as direct-to-mouth (reference).
- Treatment E: Pediatric DTG/3TC (DTG 5 mg/3TC 30 mg, 10 dispersible tablets) administered as a dispersion and taken immediately (test).
- Treatment F: Pediatric DTG/3TC (DTG 5 mg/3TC 30 mg, 10 dispersible tablets) administered as direct-to-mouth (test).

To ensure adequate washout, there will be at least 7 days between each dose of study drug, 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. In each of the 3 treatment periods, participants will be admitted to the clinic on Day −1 and will be discharged

following completion of the last study procedure on Day 4. Participants will return to the clinic for an outpatient follow-up visit 7 to 10 days after the last dose of study drug.

The total duration of participation in this study will be approximately 9 weeks. Each participant will have a screening visit within 30 days prior to the first dose of study drug, 3 treatment periods with a single dose of study drug per treatment period, and a follow-up visit within 7 to 10 days after the last dose of study drug.

Parts 1 and 2 of the study are independent of one another and may be run in parallel. Study assessments will be performed as indicated in the Schedule of Activities (SoA; Section 2).

5.2. Number of Participants

For each part, sufficient participants will be screened to achieve 18 randomized, each to 1 of 6 treatment sequences, to achieve approximately 12 evaluable participants that have completed all 3 treatment periods (2 evaluable participants per sequence; see Section 10.1).

5.3. Participant and Study Completion

A completed participant is one who has completed all phases of the study including the follow-up visit.

The end of the study is defined as the last participant's last visit.

5.4. Scientific Rationale for Study Design

The open-label crossover design of this study is well-established for evaluation of the relative BA of different oral dosage forms and random assignment to treatment sequences is an attempt to prevent bias. The washout of 7 days between dosing periods should eliminate the possibility of carryover of drug exposure from the previous dosing period. In each part of the study, there are appropriately named "test" and "reference" study treatments, which will be evaluated for the relative BA comparisons.

This study is participant to the appropriate regulatory approval and Ethics Committee approval, and will be listed on the website ClinicalTrials.gov. No blinding or placebo control will be used, as these are not necessary for the purposes of this study.

5.5. Dose Justification

The US Food and Drug Administration (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. Oral solutions, adult scored tablets, and President's Emergency Plan for AIDS Relief-approved dispersible and non-dispersible tablets of ABC and 3TC are available for use in pediatric patients, depending on their country of residence. In addition, the 10 mg DTG tablet was previously studied in study P1093 (ING112578) [GlaxoSmithKline Document Number

2015N235495_00]. The pediatric TRIUMEQ dispersible tablet consists of DTG 5 mg, ABC 60 mg, and 3TC 30 mg.

6. STUDY POPULATION

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

6.1. Inclusion Criteria

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

AGE
1. Between 18 and 65 years of age, inclusive, at the time of signing the informed consent.

TYPE OF PARTICIPANT AND DISEASE CHARACTERISTICS
2. Healthy, as determined by the investigator or medically qualified designee based on a medical evaluation, including medical history, physical examination, laboratory tests, and cardiac evaluation (history and ECG). A participant with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, outside the reference range for the population being studied may be included only if the investigator in consultation with the Medical Monitor agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study.

WEIGHT
3. Body weight ≥50 kg for males and ≥45 kg for females and body mass index (BMI) within the range 18.5 – 31.0 kg/m^2 (inclusive).

SEX
4. Male or female i. Male participants A male participant must agree to use contraception as detailed in Appendix 6 of this protocol during the treatment period and for at least 2 weeks ***plus*** an additional 90 days (a spermatogenesis cycle) after the last dose of study treatment and refrain from donating sperm during this period. ii. Female participants A female participant is eligible to participate if she is not pregnant (as confirmed by a negative serum human chorionic gonadotrophin [hCG] test), not lactating, and at least 1 of the following conditions applies: a. Non-reproductive potential, defined as:

- Premenopausal females with one of the following:
  - Documented tubal ligation
  - Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
  - Documented hysterectomy
  - Documented bilateral oophorectomy
- Postmenopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels)]. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment.

b. Reproductive potential and agrees to follow one of the options listed in the Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (see Appendix 6) from 30 days prior to the first dose of study medication and until 2 weeks after dosing with study medication and completion of the follow-up visit.

c. The investigator is responsible for ensuring that participants understand how to properly use these methods of contraception.

d. All participants participating in the study should be counselled on safer sexual practices including the use and benefit/risk of effective barrier methods (e.g., male condom) and on the risk of HIV transmission to an uninfected partner.

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

HISTORY/DIAGNOSTIC
6. For participants in Part 1 only, documentation that the participant is negative for the human leukocyte antigen (HLA)-B*5701 allele.

6.2. Exclusion Criteria

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

MEDICAL CONDITIONS
1. ALT and bilirubin >1.5 × ULN (isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin ≤35%).
2. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).

3. Exclusion criteria for screening ECG (a single repeat is allowed for eligibility determination):

	Males	Females
Heart Rate	<45 and >100 bpm[1]	<50 and >100 bpm[1]
PR Interval	<120 and >220 msec	
QRS Interval	<70 and >120 msec	
QTcF Interval[2]	>450 msec	

1. A heart rate from 100 to 110 bpm may be rechecked by ECG or vitals within 30 minutes to verify eligibility.
2. The QTcF is the QT interval corrected for heart rate according to Fridericia's formula, machine-read or manually over-read.

- Evidence of previous myocardial infarction (does not include ST segment changes associated with repolarization).
- Any conduction abnormality (including but not specific to left or right complete bundle branch block, AV block [2nd degree or higher], Wolf-Parkinson-White syndrome).
- Sinus pauses >3 seconds.
- Any significant arrhythmia which, in the opinion of the principal investigator or ViiV/GlaxoSmithKline (GSK) medical monitor, will interfere with the safety of the individual participant.
- Non-sustained or sustained ventricular tachycardia (3 consecutive ventricular ectopic beats).

NOTE:

For purposes of data analysis, only QTcF will be used as specified in the Reporting and Analysis Plan (RAP).

PRIOR/CONCOMITANT THERAPY

4. Unable to refrain from the use of prescription (e.g., dofetilide) 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 medication, unless in the opinion of the Investigator and ViiV Healthcare Medical Monitor the medication will not interfere with the study procedures or compromise participant safety.

RELEVANT HABITS

5. History of regular alcohol consumption within 6 months of the study, defined as an average weekly intake of >14 drinks for males or >7 drinks for females. One drink 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.
6. Urinary cotinine levels indicative of smoking or history or regular use of tobacco- or nicotine-containing products within 1 month prior to screening.

CONTRAINDICATIONS
7. History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates their participation. The participant has participated in a clinical trial and has received an investigational product (IP) within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the IP (whichever is longer).

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE
8. The participant has participated in a clinical trial and has received an IP within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the IP (whichever is longer).

DIAGNOSTIC ASSESSMENTS
9. Creatinine clearance (CrCL) <90 mL/min 10. Presence of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test result at Screening or within 3 months prior to first dose of study treatment. 11. A positive prestudy drug/alcohol/cotinine screen. 12. A positive test for HIV antibody. 13. Where participation in the study would result in donation of blood or blood product in excess of 500 mL within 60 days. 14. Exposure to more than four new chemical entities within 12 months prior to the first dosing day.

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

Participants will refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from 7 days before the start of study treatment until after the final dose.

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 72 hours postdose).

Once in the clinical unit, participants will not be allowed to eat anything other than the food provided by the study centre.

6.3.2. Fasting Conditions

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

- An evening meal and/or snack will be provided by the unit (e.g., on Day −1).

- From midnight, participants must then fast from all food and drink, except water (approximately 10 hours predose and prior to any clinical laboratory evaluations, except repeat evaluations).
- Water is permitted with dosing (approximately 240 mL total, including volume used for dispersing Treatments B and E) and at all times, except 1 hour predose through 2 hours postdose.
- No food is allowed for at least 4 hours postdose.

6.3.3. Fed Conditions

With the exception of the time period outlined for fasting conditions, participants will receive all other meals as defined as standard for the study centre.

6.3.4. 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 postdose.

Use of tobacco products is not allowed from 1 month prior to Screening and until after the final follow-up visit.

6.3.5. Activity

Participants will abstain from strenuous exercise for 48 hours prior to each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (e.g., watch television, read).

6.4. Screen Failures

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

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

7. TREATMENTS

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

7.1. Treatments Administered

Study Treatments				
Product name:	TRIUMEQ (Adult)	TRIUMEQ (Pediatric)	DTG and 3TC (Adult)	DTG/3TC (Pediatric)
Dosage form:	1 Conventional tablet	10 Dispersible Tablets	1 Conventional tablet of each	10 Dispersible Tablets
Unit dose strength(s)/ Dosage level(s):	Single dose, FDC tablet – DTG 50 mg/ABC 600 mg/ 3TC 300 mg	Single dose, FDC tablet – DTG 5 mg/ABC 60 mg/ 3TC 30 mg	Single dose, 1 tablet DTG (50 mg) and 1 tablet 3TC (300 mg)	Single dose, FDC tablet – DTG 5 mg/ 3TC 30 mg
Route of Administration	Oral	Oral	Oral	Oral
Dosing instructions:	**Treatment A:** Consume 1 tablet by taking directly into mouth with 240 mL of water	**Treatment B:** Disperse 10 tablets in water as described in Section 7.1.1 ("Sterile Water for Irrigation, USP" is acceptable) and consume immediately (no more than 30 minutes after preparation)[1] **Treatment C:** Consume 10 tablets by taking them directly into mouth with 240 mL of water[1]	**Treatment D:** Consume 1 tablet of each by taking directly into mouth with 240 mL of water	**Treatment E:** Disperse 10 tablets in water as described in Section 7.1.1 ("Sterile Water for Irrigation, USP" is acceptable) and consume immediately (no more than 30 minutes after preparation)[1] **Treatment F:** Consume 10 tablets by taking them directly into mouth with 240 mL of water[1]
Manufacturer:	GlaxoSmithKline	GlaxoSmithKline	GlaxoSmithKline	GlaxoSmithKline
Fasting instructions:	Administer in the AM under fasted conditions. Food will be unavailable until 4 hours postdose and water until 2 hours postdose.	Administer in the AM under fasted conditions. Food will be unavailable until 4 hours postdose and water until 2 hours postdose.	Administer in the AM under fasted conditions. Food will be unavailable until 4 hours postdose and water until 2 hours postdose.	Administer in the AM under fasted conditions. Food will be unavailable until 4 hours postdose and water until 2 hours postdose.

1. The strawberry cream (PHS-132963) flavor of TRIUMEQ and DTG/3TC dispersible tablets contains no strawberry extracts and is therefore safe for use by people who are allergic to strawberries.

7.1.1. Dosing of Dispersible Tablets in Treatments B and E

Each dispersible tablet for Treatment B contains DTG 5 mg/ABC 60 mg/3TC 30 mg; therefore, 10 tablets will be needed to achieve the DTG 50 mg/ABC 600 mg/3TC 300 mg total dose.

Each dispersible tablet for Treatment E contains DTG 5 mg/3TC 30 mg; therefore, 10 tablets will be needed to achieve the DTG 50 mg/3TC 300 mg total dose.

1. Place 50 mL of water in a 125-mL Nalgene container. A 60-mL syringe is appropriate to measure this volume. (Note: glass containers should not be used, as oxidation may occur.)

2. Place 10 tablets into the container and swirl/stir for 3 to 3.5 minutes. The tablets should be fully dispersed in approximately 90 seconds, but swirling/stirring for the full time will guarantee dispersion.
3. Have the participant swallow the dispersion as swiftly as they can, preferably in 1 to 2 swallows.
4. Rinse the container with 50 mL of water (a 60 mL syringe is appropriate to measure this volume) and have the participant swallow the rinse as swiftly as they can, preferably in 1 to 2 swallows.
5. Give the participant an additional 140 mL of water to swallow (Note: total volume of water given in Steps 1-5 should be 240 mL; additional water, if needed, will be documented).

Note the words "immediately dose" in the protocol mean within 30 minutes after completion of the 3- to 3.5-minute preparation.

Anticipate that there will still be a limited amount of insoluble material visible in the dosing container after the dispersion has been dosed and rinsed; this is normal and will not affect the dose delivered.

7.1.2. Dosing of Pediatric TRIUMEQ Tablets in Treatments C and F

Each dispersible tablet for Treatment C contains DTG 5 mg/ABC 60 mg/3TC 30 mg; therefore, 10 tablets will be needed to achieve the DTG 50 mg/ABC 600 mg/3TC 300 mg total dose.

Each dispersible tablet for Treatment F contains DTG 5 mg/3TC 30 mg; therefore, 10 tablets will be needed to achieve the DTG 50 mg/3TC 300 mg total dose.

Participants will swallow 10 pediatric TRIUMEQ tablets for Treatment C, or 10 pediatric DTG/3TC tablets for Treatment F, with 240 mL of room-temperature tap water. Additional water, if needed to consume all 10 tablets, will be documented.

7.2. Dose Modification

Not applicable.

7.3. Method of Treatment Assignment

In each part, participants will be randomized to 1 of 6 treatment sequences (ABC, BCA, CAB, ACB, BAC, or CBA in Part 1; DEF, EFD, FDE, DFE, EDF, or FED in Part 2) in accordance with the randomization schedule generated by PPD prior to the start of the study and using validated software. Descriptions of the study treatments A, B, C, D, E, and F, and the respective treatment sequences are presented in Section 5.1 of this protocol.

7.4. Blinding

This will be an open-label study.

7.5. Preparation/Handling/Storage/Accountability

The tablets are packaged in high-density polyethylene bottles. Each bottle will contain 30 tablets. Tablets must be stored in the original package with the bottle tightly closed. The bottles contain a desiccant that must be kept in the bottle to protect tablets from moisture.

The contents of the label will be in accordance with all applicable regulatory requirements.

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment, and only in accordance with the protocol. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual (SRM).
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
- A Safety Data Sheet describing the occupational hazards and recommended handling precautions will be provided to site staff. Adequate precautions must be taken to avoid direct contact with the IP.

7.6. Treatment Compliance

When participants are dosed at the site, they will receive study treatment directly from the investigator or designee under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment 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 treatment. Study site personnel will examine each participant's mouth to ensure that the study treatment was ingested.

7.7. Concomitant Therapy

Participant must abstain from taking any other prescription (i.e. dofetilide) and nonprescription 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 medication, unless in the

opinion of the investigator and ViiV Healthcare Medical Monitor the medication will not interfere with the study procedures or compromise participant safety.

Use of antacids, vitamins, and iron supplements are strictly prohibited 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 medication and for the duration of the trial, including follow-up.

Acetaminophen, at doses of ≤2 grams/day, is permitted for use any time during the study and should be noted in the electronic case report form (eCRF). Other concomitant medication may be considered on a case by case basis by the investigator in consultation with the ViiV Healthcare Medical Monitor.

7.8. Treatment after the End of the Study

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

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

8.1.1. Liver Chemistry Stopping Criteria

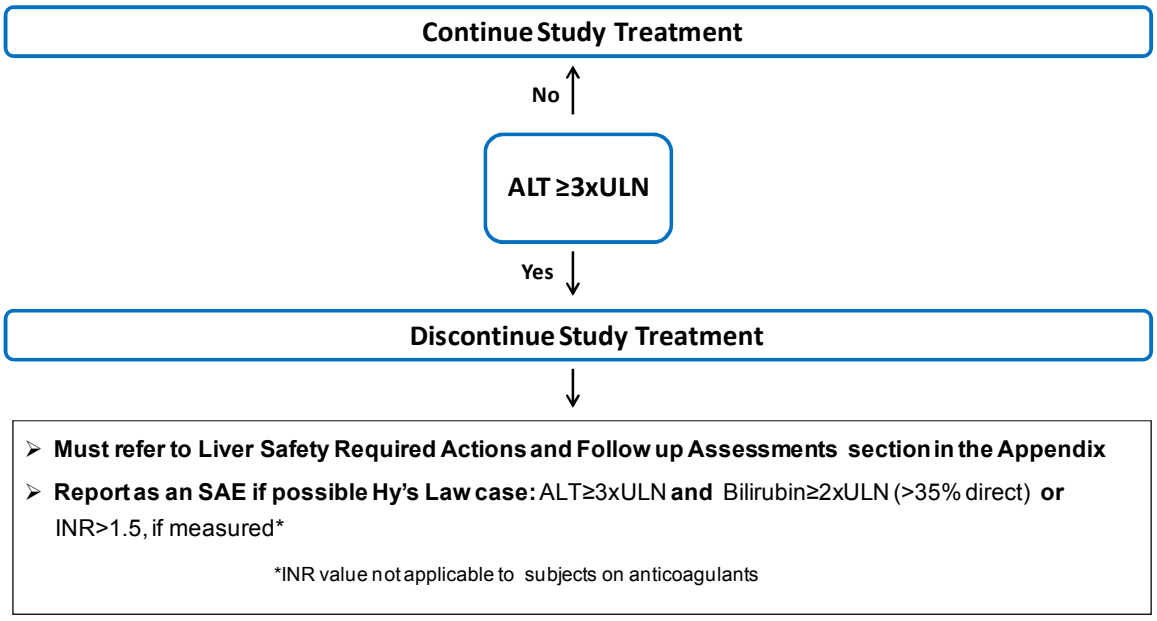
Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

NOTE: Although this is a single-dose study, please use the following as guidance:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

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

Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



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

8.1.2. QTc Stopping Criteria

A participant that meets the following bulleted criterion will be withdrawn from the study:

- QTcF > 500 msec

Notes:

- QTcF should be used for all QTc data being collected for data analysis. Safety ECGs and other non-protocol specified ECGs are an exception.
- The QTc should be based on averaged QTc values of triplicate ECGs obtained over a brief (e.g., 5 to 10 minutes) recording period.

8.2. Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons, including but not limited to:

- Participant or investigator non-compliance

- Participant requires concurrent medications after Screening that cannot be interrupted for 2 weeks prior to administration of IP and until completion of the study
- Pregnancy
- Positive urine drug or alcohol screen
- Any clinically significant adverse even (AE) deemed to require discontinuation of IP

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

Participants who withdraw, or are withdrawn from the study will not be replaced.

Refer to the SoA (Section 2) for data to be collected at the time of study discontinuation and follow-up, and for any further evaluations that need to be completed.

8.3. Lost to Follow Up

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

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

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

9. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 2) and are the same for Parts 1 and 2.

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the SoA, are essential and required for study conduct.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

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.

The following points must be noted:

- If assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order:
  1. 12-lead ECG
  2. Vital signs
  3. Blood draws

  Note: Although PK calculations will be based on the actual time of collection, the timing of the assessments should allow the blood draw to occur at the exact nominal time noted in the SoA (Section 2).

- 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.
- The change in timing or addition of time points for any planned study assessments must be documented in a Note to File that is approved by the relevant ViiV Healthcare study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment.
- The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.
- No more than 500 mL of blood will be collected over the duration of the study, including any extra assessments that may be required

9.1. Efficacy Assessments

Not applicable.

9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 8.

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study (see Section 8).

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

- Any SAE assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a ViiV Healthcare product will be recorded from the time of participant randomization up to and including any follow-up contact.
- All AEs will be collected from the time of participant randomization until the follow-up contact at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF, not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 8. 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 in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.
- 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 8.

9.2.2. 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. Appropriate questions include the following:

- “How are you feeling?”
- “Have you had any (other) medical problems since your last visit/contact?”
- “Have you taken any new medicines, other than those provided in this study, since your last visit/contact?”

9.2.3. 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, and nonserious AEs of special interest, will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 8.

9.2.4. 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 treatment 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 treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing 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 IB and will notify the IRB/IEC, if appropriate, according to local requirements.

9.2.5. Pregnancy

- Details of all pregnancies in all female participants will be collected after the start of dosing and until the final postdose follow-up visit.
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 6.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, or ectopic pregnancy) are considered SAEs.

9.3. Treatment of Overdose

For this study, any dose of DTG, ABC, and/or 3TC greater than 50 mg, 600 mg, and/or 300 mg, respectively, will be considered an overdose.

ViiV Healthcare does not recommend specific treatment for an overdose of DTG, ABC, and/or 3TC. The investigator will use clinical judgment to treat any overdose.

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

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until DTG, ABC, and/or 3TC 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 treatment if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

9.4. Safety Assessments

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

9.4.1. Physical Examinations

- A brief physical examination (Screening and Day −1 of Period 1) 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.

9.4.2. Vital Signs

- Vital signs will be measured in supine or semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure and pulse rate.

9.4.3. Electrocardiograms

- Twelve-lead ECGs will be performed with the participant in a supine or semi-supine position, having rested in this position for at least 10 minutes beforehand.
- Single 12-lead ECGs will be obtained at Screening and on Day −1 as indicated in the SoA (Section 2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 8.1.2 for QTcF withdrawal criteria and additional QTcF readings that may be necessary.

9.4.4. Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA (Section 2) for the timing and frequency.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 7 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the 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 2).

Laboratory requisition forms must be completed and samples must be clearly labelled with the participant number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the SRM (a.k.a., BioPacket). Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

If additional nonprotocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE) the results must be recorded in the eCRF.

Refer to the BioPacket for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

9.5. Pharmacokinetics

9.5.1. Blood Sample Collection

Whole blood samples of approximately 2 mL will be collected into K_2EDTA tubes for measurement of plasma concentrations of DTG, ABC, and 3TC (in Part 1); and DTG and 3TC (in Part 2) as specified in the SoA (Section 2). Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

9.5.2. Sample Analysis

Plasma analysis will be performed under the control of Platform Technology and Science (PTS), GlaxoSmithKline, the details of which will be included in the SRM (BioPacket). Concentrations of DTG, ABC, and 3TC will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the BioPacket).

Once the plasma has been analyzed for drug concentrations any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate PTS, ViiV Healthcare/GlaxoSmithKline protocol.

9.6. Formulation Palatability Assessment

A palatability questionnaire (Appendix 4) will be administered to each participant within 10 minutes following dosing of dispersion treatments only, as indicated in the SoA (Section 2). Participants will be given the questionnaire to read prior to receiving each unique dispersion dose.

9.7. Genetics

(HLA)-B*5701 allele samples in Part 1 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.

10. STATISTICAL CONSIDERATIONS

This study is designed to estimate the relative BA of each test treatment to the reference treatment (B vs. A and C vs. A in Part 1; E vs. D and F vs. D in Part 2) in the fasted state.

No formal hypotheses will be tested. For each primary PK endpoint in each part (AUC[0-∞], AUC[0-t], and Cmax), point estimates and corresponding 90% confidence intervals (CIs) will be constructed for the ratio of the geometric mean of the test treatment to the geometric mean of the reference treatment.

10.1. Sample Size Determination

10.1.1. Sample Size Assumptions

The PK of DTG is expected to have greater variability than ABC and 3TC; therefore, the sample size calculation is based upon estimates of DTG PK variability. Based on the results from a previous PK study of DTG granules administered to healthy volunteers, [GlaxoSmithKline Document Number 2011N124158_00], the within participant variability (CVw%) of DTG AUC(0-∞) and Cmax ranged from 15.0% to 16.2%. Therefore, it is decided that 16.2% would be a conservative estimate on which the sample size calculation is based.

For each study part, with a sample size of 12 evaluable participants (2 participants/sequence), it is estimated that the precision (i.e. half-width of the 90% CI on the ratio scale) for the test: reference comparison will be within 12.5% of the point estimate for AUC(0-∞) and Cmax. Hence, if the point estimate of the ratio of geometric means is 1, then the 90% CI will be approximately (0.89, 1.13).

10.1.2. Sample Size Sensitivity

For the sensitivity analysis, assuming a higher within-participant variability (24%), a sample size of 12 evaluable participants in each study part, it is estimated that the half width of the 90% CI for the ratio of treatment comparison (test: reference) would be within 19.0% of the point estimate for AUC(0-∞) and Cmax.

10.2. Populations for Analyses

Participants excluded from any analyses will be fully documented and justified within the clinical study report (CSR). All analyses will be based on the actual treatment that each participant received. Any departures from the planned treatment according to the randomization schedule will be documented in the CSR.

For purposes of analysis, the following populations are defined for each part:

Population	Description
All Participants	All participants who receive at least 1 dose of study medication. This population will be used for all demographic and safety summaries.

Population	Description
Pharmacokinetic (PK)	Participants in the 'All Participants' population for whom a PK sample was obtained and who had evaluable PK assay results. Pharmacokinetic samples that may be affected by protocol deviations will be reviewed by the study team to determine whether or not the sample will be excluded. This population will be used for reporting of PK data.

10.3. Statistical Analyses

10.3.1. Key Elements of Analysis Plan

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

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

Unless stated otherwise, descriptive summaries for continuous variables in each part will include *n*, mean, standard deviation (SD), coefficient of variation for the mean (%CV), median, minimum, and maximum. Categorical variables will be summarized with *n* and percent. Geometric mean with associated 95% CI and the between-participant CV (%CVb) for the geometric mean will be included for PK variables, where applicable.

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

SAS Version 9.3 or higher will be used to analyze data, as well as to generate tables, listings, and figures.

10.3.2. Pharmacokinetic Analyses

Pharmacokinetic analyses will be performed under the supervision of the Clinical Pharmacology Modeling & Simulation department within GSK or their designee. For Part 1, plasma DTG, ABC, and 3TC; and, for Part 2, DTG and 3TC concentration-time data will be analyzed by noncompartmental methods with Phoenix WinNonlin Version 6.4 or higher. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following PK parameters will be determined, as data permit: Cmax, Tmax, Tlast, AUC(0-t), AUC(0-24), AUC(0-∞), t1/2, tlag, C24, Ct, Vz/F, and CL/F.

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

Statistical analyses of the PK parameter data will be the responsibility of Clinical Pharmacology, PPD.

The primary PK parameters for DTG, ABC, and 3TC in Part 1; and DTG and 3TC in Part 2 (AUC[0-∞], AUC[0-t], and Cmax) will be $\log_e$-transformed and separately analyzed using a mixed-effects model with fixed-effect terms for Period, Treatment, and Treatment Sequence for each treatment comparison. Participant will be nested within Treatment Sequence and treated as a random effect in the model. Point estimates and their associated 90% CIs will be constructed for the differences in PK parameter values between test and reference treatments. The point estimates and their associated 90% CIs will then be back-transformed to provide point estimates and 90% CIs for the ratios of PK parameters from test and reference treatments.

Further details will be provided in the RAP.

10.3.3. Safety Analyses

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

The details of the statistical analyses of safety will be provided in the RAP.

10.3.4. Other Analyses

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

10.3.5. Interim Analyses

There will be no formal interim analysis.

11. REFERENCES

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

%CV	Coefficient of variance
%CVb	Between participant coefficient of variation
3TC	Lamivudine
ABC	Abacavir
AE	Adverse event
AIDS	Acquired immune deficiency syndrome
ALT	Alanine transaminase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC(0-∞)	Area under the concentration-time curve from time zero extrapolated to infinity
AUC(0-24)	Area under the plasma concentration-time curve from time of dose to 24 hours
AUC(0-t)	Area under the concentration-time curve 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
BMI	Body mass index
CIOMS	Council for International Organizations of Medical Sciences
C24	Observed concentration at 24 hours after dose administration
CI	Confidence interval
CL/F	Apparent total clearance
Cmax	Maximum observed plasma concentration
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CSR	Clinical study report
Ct	Last observed quantifiable concentration
DAIDS	Division of AIDS
dL	Deciliter
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
hCG	Human chorionic gonadotropin
HIPPA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HRT	Hormone replacement therapy
HSR	Hypersensitivity Reaction
IB	Investigator's Brochure
ICF	Informed consent form
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
INI	Integrase inhibitor
INR	International normalized ratio
IP	Investigational product(s)
IRB	Institutional Review Board
kg	Kilogram
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
µMol	Micromolar
MCH	Hemoglobin amount per red blood cell
MCV	Average red blood cell size
mg	Milligrams
mL	Milliliter
mmHg	Millimeters of mercury
PK	Pharmacokinetic(s)
PTS	Platform Technology and Science
QTc	Corrected QT interval
QTcF	Corrected QT interval according to Fridericia's formula
RAP	Reporting and analysis plan
RBC	Red blood cells
SAE	Serious adverse event
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SoA	Schedule of Activities
SRM	Study reference manual
SUSAR	Suspected unexpected serious adverse reaction
t1/2	Terminal elimination phase half-life
tlag	Plasma lag time for absorption
Tlast	Time of last quantifiable concentration taken directly from the concentration time profile
Tmax	Time to maximum observed concentration taken directly from the concentration time profile
ULN	Upper limit of normal

US	United States
Vz/F	Apparent volume of distribution during the terminal phase following extravascular administration
WBC	White blood cells

Trademark Information

Trademarks of ViiV Healthcare
KIVEXA/EPZICOM
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12.2. Appendix 2: Clinical Laboratory Tests

Hematology, clinical chemistry, urinalysis, and additional parameters to be tested are listed in Table 1.

- The tests detailed in Table 1 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of this 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 Assessments

Laboratory Assessments	Parameters			
Haematology	Platelet Count RBC Count Hemoglobin Hematocrit	*Red Blood Cell (RBC) Indices*: Mean corpuscular volume (MCV) Mean corpuscular haemoglobin (MCH)		*White blood cell (WBC) count with Differential*: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry [1]	Blood urea nitrogen (BUN) Creatinine Glucose	Potassium Sodium Calcium	Aspartate aminotransferase (AST [SGOT]) ALT (SGPT) Alkaline phosphatase Creatine phosphokinase (CPK)	Total and direct bilirubin Total Protein Albumin
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood and ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• HIV • Hepatitis B (HBsAg) • Hepatitis C (Hep C antibody) • FSH and estradiol • Alcohol, cotinine, and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Urine Pregnancy test (for WOCBP) • HLA-B*5701 screening for Part 1 • Creatine clearance (CrCL) 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 8.1.1 Liver Chemistry Stopping Criteria

12.3. Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- 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.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

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

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations,

ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

The ICF may contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research in accordance with SOP-GSKF-410. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. 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 remaining specimens to be used for exploratory research. Participants who decline to participate will not provide this separate signature.

Data Protection

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

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 multicentre 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.

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 ViiV Healthcare site or other mutually-agreeable location.
- ViiV Healthcare will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.
- The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with ViiV Healthcare Policy.

Data Quality Assurance

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

Source Documents

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

Study and Site Closure

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

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

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

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

12.4. Appendix 4: Palatability Questionnaire

The following questionnaire will be administered to each participant within 10 minutes following any dose given as dispersion. Participants will be given the questionnaire to read prior to receiving this dose.
Participant #: _____ Date: _____ Treatment:_____

1. Please briefly describe the taste of the product in your own words (one word, short phrase descriptions are acceptable).

2. Please rate the palatability (acceptability of taste) of the product by checking a rating below.

____1 = unacceptable (would not use product under any circumstances)
____2 = neutral/acceptable
____3 = very good

3. Please check **all** the descriptors that apply to the product.

_____ Sweet

_____ Sour/tart

_____ Bitter

_____ Fruity

_____ Nutty

_____ Chalky

_____ Medicinal

4. Please select the descriptor you most closely associate with the flavor of the product (i.e., select one).

_____ Sweet

_____ Sour/tart

_____ Bitter

_____ Fruity

_____ Nutty

_____ Chalky

_____ Medicinal

_____ Other (please specify)_____

Participant #: _____ Date: _____ Treatment:_____

5. Please rate the mouth feel of the product by checking a rating below.

_____ 1= unacceptable (would not use product under any circumstances)
_____ 2= neutral/acceptable
_____ 3= very good

6. Please rate the aroma of the product by checking a rating below.

____1 = unpleasant/unacceptable aroma
____2 = neutral/acceptable aroma
____3 = pleasant/desirable aroma

7. Please rate the product aftertaste by checking a rating below.

____1 = unpleasant/unacceptable (e.g. need/desire to wash taste out of mouth)
____2 = neutral/acceptable
____3 = pleasant/desirable

Participant #: _____ Date: _____ Treatment:_____

8. For each of the following attributes please circle the number that best describes your perception of each attribute.

a. Flavor intensity Mild Average Strong

1 2 3 4 5

b. Aroma Mild Average Strong

1 2 3 4 5

c. Sweetness Not Sweet Sweet Very Sweet

1 2 3 4 5

d. Sour/tartness Mild Average Strong

1 2 3 4 5

e. Consistency Thin Average Thick

1 2 3 4 5

Participant #: _____ Date: _____ Treatment:_____

9. Based on your response to #8, please circle the number on a scale of 1 to 5 that best describes your recommendation for modifying this product where:

   1 = Reduce as much as possible
   3 = Leave as is
   5 = Increase as much as possible

f. Flavor intensity **Reduce** **Leave as is** **Increase**

1 2 3 4 5

g. Aroma

1 2 3 4 5

h. Sweetness

1 2 3 4 5

i. Sour/tartness

1 2 3 4 5

j. Consistency

1 2 3 4 5

10. Please rate the color of the product on a scale of 1 to 3, where:

____1 = unpleasant
____2 = neutral/acceptable
____3 = pleasant/desirable

11. Do you have any other suggestions for changing/improving the flavor of this product?

12.5. Appendix 5: 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 9). Additional information regarding detecting, documenting and reporting AEs and SAEs are available in Appendix 8.

Study drug may be interrupted at the discretion of the investigator and according to the severity of the AE. If one or more ART medication is held due to toxicity or AEs, all ART medications should be held to reduce the risk of development of resistance taking into account the length of the planned interruptions and the PK half-life of each ART of the regimen, in order to minimize the risk of development of resistance.

No toxicity-related dose reductions of study drugs will be allowed. Study drugs should be restarted as soon as medically appropriate; in general, this should be no longer than 4 weeks after interruption (unless Grade 3 or 4 toxicities persist). Decisions regarding sequential reintroduction of study drugs or temporary interruption of one but not all drugs within the ART regimen should be made with the understanding that these changes may result in incomplete viral suppression and selection of resistant virus. Guidance is provided below on participant management and study drug interruptions based on the severity of the AE for specific toxicities. All changes in study drug must be accurately recorded in the participant's eCRF.

NOTE: In the event of a discontinuation of DTG/ABC/3TC FDC for any reason, re-initiation of this drug should be undertaken with caution. 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 HSR, and initiate participant management as outlined in the DTG IB, regardless of a participant'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 treatment 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 treatment, 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 drugs should have study treatment withheld and be rechecked each week until the AE returns to Grade 2. Once the AE is Grade ≤2, study treatment may be restarted.

Should the same Grade 3 AE recur within 28 days in the same participant, study treatment should be permanently discontinued and the participant withdrawn from study. Participants experiencing Grade 3 AEs requiring permanent discontinuation of study treatment should be followed weekly until resolution of the AE and have withdrawal study evaluations completed. A Follow-up visit should be performed 4 weeks after the last dose of study drugs.

Participants with asymptomatic Grade 3 laboratory abnormalities should be investigated for all potential non-drug related causes, and, following discussion with the medical monitor, may continue study drug if the investigator has compelling evidence that the toxicity is not related to study treatment.

Exceptions are noted for rash in Section 12.5.8.

Grade 4 Toxicity/Adverse Event

Participants who develop a Grade 4 AE or toxicity should have study treatment discontinued. However, if the investigator has compelling evidence that the AE is not causally related to the study drugs, dosing may continue after discussion with and assent from the medical monitor. Participants should be rechecked each week until the AE returns to Grade 2.

Participants experiencing Grade 4 AEs requiring permanent discontinuation of study treatment 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 should be investigated for all potential non-drug related causes, and, following discussion with the medical monitor, may continue therapy if the investigator has compelling evidence that the toxicity is not related to study treatment. An in-clinic Follow-Up visit will be conducted approximately 4 weeks after the last dose of study medication for participants with ongoing AEs, and SAEs and also any laboratory abnormalities that are considered to be AEs or potentially harmful to the participant, at the last on-study visit.

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 treatment for reasons of toxicity should be followed weekly until resolution of the AE and encouraged to complete the withdrawal and Follow-up study evaluations (see Section 9.2.3).

12.5.1. 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 total protein/albumin 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 SPM 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.

12.5.2. Hypersensitivity Reaction

Both ABC and DTG are associated with a risk for hypersensitivity reactions (HSR), and share some common features such as fever and/or rash with other symptoms indicating multi-organ involvement. Clinically it is not possible to determine whether a HSR 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 IB [GlaxoSmithKline Document Number RM2007/00683/11].

The risk for ABC HSR to occur is significantly increased for patients who test positive for the *HLA-B*5701* allele. However, ABC HSRs 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 HSR 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 participants who were *HLA-B*5701* negative and who received ABC developed a clinically suspected ABC HSR, respectively [Post, 2010; Squires, 2010].

With reference to the DTG/ABC/3TC IB and the 'Participant Information and Consent Form', Investigators must ensure that participants are fully informed regarding the risk of HSR 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/3TCmust be stopped without delay, even in the absence of the HLA-B*5701 allele, if a HSR is suspected. Delay in stopping treatment after the onset of hypersensitivity may result in a life-threatening reaction.** Clinical status including liver aminotransferases and bilirubin should be monitored.
- Participants who have experienced a hypersensitivity reaction should be instructed to dispose of their remaining tablets, in order to avoid restarting ABC.
- **After stopping treatment with DTG/ABC/3TC for reasons of a suspected HSR, DTG/ABC/3TC or any other medicinal product containing ABC or DTG must never be re-initiated.**

- **Restarting ABC- containing products following a suspected ABC HSR can result in a prompt return of symptoms within hours and may include life-threatening hypotension and death.**
- **If a hypersensitivity reaction is ruled out, Participants may restart DTG/ABC/3TC. Rarely, patients who have stopped ABC for reasons other than symptoms of HSR have also experienced life-threatening reactions within hours of re- initiating abacavir therapy. Participants must be made aware that HSR can occur with reintroduction of DTG/ABC/3TC or any other medicinal product containing abacavir and that reintroduction of DTG/ABC/3TC or any other medicinal product containing abacavir should be undertaken only if medical care can be readily accessed.**

Reporting of Hypersensitivity Reactions

If a clinically suspected case of HSR to ABC meets one of the International Conference on Harmonization (ICH)-E2A definitions of seriousness listed in Appendix 8 then, in addition to reporting the case as an SAE, the ABC HSR CRF should also be completed within one week of the onset of the hypersensitivity reaction.

12.5.3. Skin Reactions without Other Symptoms that are Typical of ABC HSR

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.

Participants who develop rash of any grade should be evaluated for the possibility of an ABC HSR or a serious skin reaction such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) or Erythema Multiforme. SJS, TEN 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 HSR, but they do have features typical of these serious skin reactions.

If a serious skin reaction develops, ABC (and / or all other concurrent medication(s) suspected in the Investigators causality assessment) should be discontinued, and the participant should not be re-challenged with any ABC-containing medicinal product (i.e., TRIUMEQ, ZIAGEN™, TRIZIVIR™, EPZICOM or KIVEXA).

As many products other than abacavir also cause rash and/or serious skin reactions, all other medicinal products that the participant is receiving should also be reviewed and discontinued as appropriate.

Mild to moderate rash is an expected adverse reaction for DTG- containing ART. Episodes generally occur within the first ten weeks of treatment, rarely require

interruptions or discontinuations of therapy and tend to resolve within two to three 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 SJS, TEN 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 HSR, systemic or allergic symptoms or signs of mucosal or target lesions.

Participants with an isolated Grade 1 rash may continue IP and background ART 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 continue IP and background ART for an isolated Grade 2 rash. However, IP and background ART (and all other concurrent medication(s) suspected in the Investigators causality assessment) should be permanently discontinued for any Grade ≥2 rash that is associated with an increase in ALT (see Section 8.1.1). The participant should be advised to contact the physician immediately if rash fails to resolve (after more than two 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 IP and background ART (and all other concurrent medication(s) suspected in the Investigators causality assessment) 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 (see Section 9.2) and appropriate toxicity ratings should be used to grade the events (based on DAIDS toxicity grading).

If the etiology of the rash can be definitely diagnosed as being unrelated to IP and due to a specific medical event or a concomitant non-study medication, routine management should be performed and documentation of the diagnosis provided.

12.5.4. 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 treatment. 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. For persistent Grade 4 CPK elevations that are considered possibly or probably related to the study drugs, study treatment should be discontinued and the participant withdrawn from the study.

12.5.5. Anemia

Grade 1 (mild) hemoglobin decrease:

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

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

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

Grade 2 (moderate) hemoglobin decrease:

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

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

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

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

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

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

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

12.5.6. Total Bilirubin Elevation

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

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

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

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

12.5.7. AST and ALT Elevation

See Appendix 7.

12.5.8. Rash

Grade 1 rash (localized macular rash):

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

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

In the absence of the above signs or symptoms, participants with Grade 1 rash may continue the study drug at the discretion of the Investigator. The participant should be advised to contact the Investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms worsen, or if mucosal ulceration develops. If the rash is considered to be most likely due to concomitant illness or non-study medication, standard management, including discontinuation of the likely causative agent, should be undertaken. If no other causative factor is found after clinical evaluation, the participant may be treated symptomatically until the rash resolves. Antihistamines, topical corticosteroids or antipruritic agents may be prescribed. The participant should remain on the study to be followed for safety and PK as outlined in Section 9.2.3.

Grade 2 rash (diffuse macular, maculopapular, or morbilliform rash OR target lesions):

Participants with Grade 2 rash should be evaluated by the Investigator immediately. Digital photographs should be obtained. A dermatologist may be consulted and a biopsy may be obtained if recommended by the dermatologist. The study drug should be permanently discontinued if the following signs or symptoms are noted at any time:

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

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

antipruritic agents may be prescribed. The participant should remain on the study to be followed for safety and PK as outlined in Section 9.2.3.

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

Participants with a Grade 3 rash will permanently discontinue the study medication. The participant should be evaluated in the physician's office immediately and should be seen in the physician's office or contacted by phone every 2 days until the rash resolves. A dermatologist should be consulted and digital photographs and a biopsy should be obtained. Antihistamines, topical corticosteroids or antipruritic agents may be prescribed at the discretion of the Investigator. The participant should be advised to contact the Investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms appear, or if mucosal involvement develops. The participant should remain on the study to be followed for safety and PK as outlined in Section 9.2.3.

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

Participants with a Grade 4 rash will permanently discontinue the study medication. A dermatologist should be consulted and digital photographs and a biopsy should be obtained. Sponsor and ViiV Healthcare Medical Monitor should be notified of this serious adverse event within 24hr via phone or fax. The participant should be closely followed every day until resolution of the reaction. The participant should remain on the study to be followed for safety and PK as outlined in Section 9.2.3.

12.5.9. Allergic Reaction

Grade 1 allergic reaction (pruritus without rash):

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

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

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

corticosteroids or antipruritic agents may be prescribed. The participant should remain on the study to be followed for safety and PK as outlined in Section 9.2.3.

Grade 2 allergic reaction (localized urticaria):

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

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

In the absence of the above signs or symptoms, participants with Grade 2 allergic reaction may continue the study drug at the discretion of the Investigator. The participant should be advised to contact the Investigator immediately if there is any worsening of the allergic reaction and/or if any systemic signs or symptoms worsen. If the allergic reaction is considered to be most likely due to concomitant illness or non-study medication, standard management, including discontinuation of the likely causative agent, should be undertaken. If no other causative factor is found after clinical evaluation, the participant may be treated symptomatically until the rash resolves. Antihistamines, topical corticosteroids or antipruritic agents may be prescribed. The participant should remain on the study to be followed for safety and PK as outlined in Section 9.2.3.

Grade 3 allergic reaction (generalized urticaria or angioedema):

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

Grade 4 allergic reaction (anaphylaxis):

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

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

12.6. Appendix 6: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with ONE of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-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 enrolment.

Contraception Guidance

Male participants

- Male participants with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in Section 6.1:
  - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
  - Agree to use a male condom plus an additional method of contraception with a failure rate of <1% per year as described in Table 2 when having penile-vaginal intercourse with a woman of childbearing potential

- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 2.

Table 2 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[b] • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
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 drug. 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.)*

NOTES:

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case two highly effective methods of contraception should be utilized during the treatment period and until the completion of the follow-up visit.

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test
- Additional pregnancy testing should be performed prior to dosing in each cohort during the treatment period and as required locally
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected
- Pregnancy testing, with a sensitivity of 10 mIU/mL will be performed [and assayed in a certified laboratory OR and assayed in the central laboratory OR using the test kit provided by the central laboratory/provided by the sponsor/approved by the sponsor and in accordance with instructions provided in its package insert

Collection of Pregnancy Information

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study. This applies only to participants who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to ViiV Healthcare within 24 hours of learning of the partner's pregnancy.
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to ViiV Healthcare
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to ViiV Healthcare within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to ViiV Healthcare. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator will be reported to ViiV Healthcare as described in Appendix 8. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

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

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

Phase I Liver chemistry stopping criteria have been designed to assure participant safety and to evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Phase I liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria – Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT≥3xULN
If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or INR >1.5, Report as an SAE.
See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="3">Required Actions and Follow up Assessments following Liver Stopping Event</th></tr>
<tr><th>Actions</th><th colspan="2">Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study treatment
• Report the event to ViiV Healthcare within 24 hours
• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)
MONITORING:
If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs
• Monitor participants twice weekly until liver chemistries resolve, stabilise or return to within baseline
• A specialist or hepatology consultation is recommended
If ALT≥3xULN AND bilirubin < 2xULN and INR ≤1.5:
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24-72 hrs
• Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline</td><td colspan="2">• Viral hepatitis serology[3]
• Blood sample for pharmacokinetic (PK) analysis, obtained within 72 hours of last dose.
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.
• Record alcohol use on the liver event alcohol intake case report form

If ALT≥3xULN AND bilirubin ≥ 2xULN or NR >1.5:
• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins).
• Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009].
• Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.</td></tr>
</table>

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

12.8. Appendix 8: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

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 treatment, whether or not considered related to the study treatment. • 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 treatment.

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 treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment 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. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE.

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.

Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:
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 detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording 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 in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to ViiV Healthcare in lieu of completion of the ViiV Healthcare /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by ViiV Healthcare. 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 ViiV Healthcare.
- 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

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 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 sufficiently 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.

  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 treatment 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 treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to ViiV Healthcare. 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 ViiV Healthcare.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by ViiV Healthcare 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 ViiV Healthcare with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to ViiV Healthcare within 24 hours of receipt of the information.

Reporting of SAE to ViiV Healthcare

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

SAE Reporting to ViiV Healthcare via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the **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 CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in Medical Monitor Name and Contact Information section of the Title Page of this protocol.

12.9. Appendix 9: Division Of AIDS Table For Grading The Severity Of Adult And Paediatric Adverse Events Version 2.0, November 2014

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
ESTIMATING SEVERITY GRADE				
Clinical adverse event NOT identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention not indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
CARDIOVASCULAR				
Arrhythmia (by ECG or physical examination) *Specify type, if applicable*	No symptoms AND No intervention indicated	No symptoms AND non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Blood Pressure Abnormalities[1] **Hypertension** (with the lowest reading taken after repeat testing during a visit) *≥ 18 years of age*	140 to < 160 mmHg systolic OR 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
< 18 years of age	> 120/80 mmHg	≥ 95th to < 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥ 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Cardiac Ischemia or Infarction Report only one	NA	NA	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR Intervention indicated (e.g., oxygen)	Life-threatening consequences OR Urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)
Hemorrhage (with significant acute blood loss)	NA	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤ 2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children, packed RBCs > 10 cc/kg) indicated
Prolonged PR Interval or AV Block Report only one > 16 years of age	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
≤ 16 years of age	1st degree AV block (PR interval > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
Prolonged QTc Interval[2]	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds OR ≥ 0.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism Report only one	NA	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)
DERMATOLOGIC				
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA
Pruritus[3] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
Rash Specify type, if applicable	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis
ENDOCRINE AND METABOLIC				
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication Treatment	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma, end organ failure)
Gynecomastia	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy[4]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA
Lipohypertrophy[5]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA
GASTROINTESTINAL				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Bloating or Distension Report only one	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea ≥ 1 year of age	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Dysphagia or Odynophagia Report only one and specify location	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)
Mucositis or Stomatitis Report only one and specify location	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Nausea	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Perforation (colon or rectum)	NA	NA	Intervention indicated	Life-threatening consequences
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NA	NA
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
MUSCULOSKELETAL				
Arthralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	No symptoms but with radiographic findings AND No operative intervention indicated	Bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
Osteopenia[6] ≥ 30 years of age	BMD t-score -2.5 to -1	NA	NA	NA

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
< 30 years of age	BMD z-score -2 to -1	NA	NA	NA
Osteoporosis[6] ≥ 30 years of age	NA	BMD t-score < -2.5	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
< 30 years of age	NA	BMD z-score < -2	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
NEUROLOGIC				
Acute CNS Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
Altered Mental Status (for Dementia, see Cognitive, Behavioral, or Attentional Disturbance below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR Obtundation OR Coma
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, Behavioral, or Attentional Disturbance (includes dementia and attention deficit disorder) Specify type, if applicable	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
Developmental Delay < *18 years of age* Specify type, if applicable	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function
Neuromuscular Weakness (includes myopathy and neuropathy) Specify type, if applicable	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (includes paresthesia and painful neuropathy) Specify type, if applicable	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizures New Onset Seizure ≥ 18 years of age	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
< 18 years of age (includes new or pre-existing febrile seizures)	Seizure lasting < 5 minutes with < 24 hours postictal state	Seizure lasting 5 to < 20 minutes with < 24 hours postictal state	Seizure lasting ≥ 20 minutes OR > 24 hours postictal state	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Pre-existing Seizure	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., severity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Syncope	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NA

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
PREGNANCY, PUERPERIUM, AND PERINATAL				
Fetal Death or Stillbirth (report using mother's participant ID) Report only one	NA	NA	Fetal loss occurring at ≥ 20 weeks gestation	NA
Preterm Delivery[7] (report using mother's participant ID)	Delivery at 34 to < 37 weeks gestational age	Delivery at 28 to < 34 weeks gestational age	Delivery at 24 to < 28 weeks gestational age	Delivery at < 24 weeks gestational age
Spontaneous Abortion or Miscarriage[8] (report using mother's participant ID) Report only one	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA
PSYCHIATRIC				
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early	Moderate difficulty falling asleep, staying asleep, or waking up early	Severe difficulty falling asleep, staying asleep, or waking up early	NA
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) Specify disorder	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions
Suicidal Ideation or Attempt Report only one	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated	Suicide attempted

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
RESPIRATORY				
Acute Bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥ 70 to < 80% OR Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50 to < 70% OR Symptoms with intervention indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Forced expiratory volume in 1 second or peak flow 25 to < 50% OR Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow < 25% OR Life-threatening respiratory or hemodynamic compromise OR Intubation
Dyspnea or Respiratory Distress Report only one	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 to < 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)
SENSORY				
Hearing Loss ≥ 12 years of age	NA	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (> 80 dB at 2 kHz and above) OR Non-serviceable hearing (i.e., >50 dB audiogram and <50% speech discrimination)
< 12 years of age (based on a 1, 2, 3, 4, 6 and 8 kHz audiogram)	> 20 dB hearing loss at ≤ 4 kHz	> 20 dB hearing loss at > 4 kHz	> 20 dB hearing loss at ≥ 3 kHz in one ear with additional speech language related services indicated (where available) OR Hearing loss sufficient to indicate therapeutic intervention, including hearing aids	Audiologic indication for cochlear implant and additional speech-language related services indicated (where available)
Tinnitus	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	NA

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Uveitis	No symptoms AND Detectable on examination	Anterior uveitis with symptoms OR Medicamylasal intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions
Visual Changes (assessed from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)
SYSTEMIC				
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cytokine Release Syndrome[9]	Mild signs and symptoms AND Therapy (i.e., antibody infusion) interruption not indicated	Therapy (i.e., antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤ 24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Fatigue or Malaise Report only one	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0 to < 38.6°C or 100.4 to < 101.5°F	≥ 38.6 to < 39.3°C or ≥ 101.5 to < 102.7°F	≥ 39.3 to < 40.0°C or ≥ 102.7 to < 104.0°F	≥ 40.0°C or ≥ 104.0°F

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pain[10] (not associated with study agent injections and not specified elsewhere) Specify location	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated
Serum Sickness[11]	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (e.g., antihistamines)	Severe signs and symptoms AND Higher level intervention indicated (e.g., steroids or IV fluids)	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Underweight[12] > 5 to 19 years of age	NA	WHO BMI z-score < -2 to ≤ -3	WHO BMI z-score < -3	WHO BMI z-score < -3 with life-threatening consequences
2 to 5 years of age	NA	WHO Weight-for-height z-score < -2 to ≤ -3	WHO Weight-for-height z-score < -3	WHO Weight-for-height z-score < -3 with life-threatening consequences
< 2 years of age	NA	WHO Weight-for-length z-score < -2 to ≤ -3	WHO Weight-for-length z-score < -3	WHO Weight-for-length z-score < -3 with life-threatening consequences
Weight Loss (excludes postpartum weight loss)	NA	5 to < 9% loss in body weight from baseline	≥ 9 to < 20% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
URINARY				
Urinary Tract Obstruction	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences
SITE REACTIONS TO INJECTIONS AND INFUSIONS				
Injection Site Pain or Tenderness Report only one	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Injection Site Erythema or Redness[13] Report only one > 15 years of age	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter OR ≥ 100 cm2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
≤ 15 years of age	≤ 2.5 cm in diameter	> 2.5 cm in diameter with < 50% surface area of the extremity segment involved (e.g., upper arm or thigh)	≥ 50% surface area of the extremity segment involved (e.g., upper arm or thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling Report only one > 15 years of age	Same as for **Injection Site Erythema or Redness,** > *15 years of age*	Same as for **Injection Site Erythema or Redness,** > *15 years of age*	Same as for **Injection Site Erythema or Redness,** > *15 years of age*	Same as for **Injection Site Erythema or Redness,** > *15 years of age*
≤ 15 years of age	Same as for **Injection Site Erythema or Redness,** ≤ *15 years of age*	Same as for **Injection Site Erythema or Redness,** ≤ *15 years of age*	Same as for **Injection Site Erythema or Redness,** ≤ *15 years of age*	Same as for **Injection Site Erythema or Redness,** ≤ *15 years of age*
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in < 48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA
LABORATORY VALUES Chemistries				
Acidosis	NA	pH ≥ 7.3 to < LLN	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to < LLN *30 to < LLN*	≥ 2.0 to < 3.0 *≥ 20 to < 30*	< 2.0 *< 20*	NA
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Alkalosis	NA	pH > ULN to ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
ALT or SGPT, High Report only one	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High Report only one	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
AST or SGOT, High Report only one	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to < LLN *16.0 to < LLN*	11.0 to < 16.0 *11.0 to < 16.0*	8.0 to < 11.0 *8.0 to < 11.0*	< 8.0 *< 8.0*
Bilirubin Direct Bilirubin[14], High > 28 days of age	NA	NA	> ULN	> ULN with life-threatening consequences (e.g., signs and symptoms of liver failure)
≤ 28 days of age	ULN to ≤ 1 mg/dL	> 1 to ≤ 1.5 mg/dL	> 1.5 to ≤ 2 mg/dL	> 2 mg/dL
Total Bilirubin, High > 28 days of age	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
≤ 28 days of age	Total Bilirubin for Term and Preterm Neonates	Total Bilirubin for Term and Preterm Neonates	Total Bilirubin for Term and Preterm Neonates	Total Bilirubin for Term and Preterm Neonates
Calcium, High (mg/dL; *mmol/L*) ≥ 7 days of age	10.6 to < 11.5 *2.65* to < *2.88*	11.5 to < 12.5 *2.88* to < *3.13*	12.5 to < 13.5 *3.13* to < *3.38*	≥ 13.5 ≥ *3.38*
< 7 days of age	11.5 to < 12.4 *2.88* to < *3.10*	12.4 to < 12.9 *3.10* to < *3.23*	12.9 to < 13.5 *3.23* to < *3.38*	≥ 13.5 ≥ *3.38*
Calcium (Ionized), High (mg/dL; *mmol/L*)	> ULN to < 6.0 *> ULN to < 1.5*	6.0 to < 6.4 *1.5 to < 1.6*	6.4 to < 7.2 *1.6 to < 1.8*	≥ 7.2 ≥ *1.8*
Calcium, Low (mg/dL; *mmol/L*) ≥ 7 days of age	7.8 to < 8.4 *1.95* to < *2.10*	7.0 to < 7.8 *1.75* to < *1.95*	6.1 to < 7.0 *1.53* to < *1.75*	< 6.1 *< 1.53*
< 7 days of age	6.5 to < 7.5 *1.63* to < *1.88*	6.0 to < 6.5 *1.50* to < *1.63*	5.50 to < 6.0 *1.38* to < *1.50*	< 5.50 *< 1.38*
Calcium (Ionized), Low (mg/dL; *mmol/L*)	< LLN to 4.0 *< LLN to 1.0*	3.6 to < 4.0 *0.9 to < 1.0*	3.2 to < 3.6 *0.8 to < 0.9*	< 3.2 *< 0.8*

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine Kinase, High	3 to < 6 x ULN	6 to < 10 x ULN	10 to < 20 x ULN	≥ 20 x ULN
Creatinine, High	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase of > 0.3 mg/dL above baseline	> 1.8 to < 3.5 x ULN OR Increase of 1.5 to < 2.0 x above baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x above baseline
Creatinine Clearance[15] or eGFR, Low Report only one	NA	< 90 to 60 ml/min or ml/min/1.73 m2 OR 10 to < 30% decrease from baseline	< 60 to 30 ml/min or ml/min/1.73 m2 OR ≥ 30 to < 50% decrease from baseline	< 30 ml/min or ml/min/1.73 m2 OR ≥ 50% decrease from baseline or dialysis needed
Glucose (mg/dL; *mmol/L*) Fasting, High	110 to 125 *6.11 to < 6.95*	> 125 to 250 *6.95 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	> 500 *≥ 27.75*
Nonfasting, High	116 to 160 *6.44 to < 8.89*	> 160 to 250 *8.89 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	> 500 *≥ 27.75*
Glucose, Low (mg/dL; *mmol/L*) ≥ 1 month of age	55 to 64 *3.05 to 3.55*	40 to < 55 *2.22 to < 3.05*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
Lactate, High	ULN to < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences
Lipase, High	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
Lipid Disorders (mg/dL; *mmol/L*) Cholesterol, Fasting, High ≥ 18 years of age	200 to < 240 *5.18 to < 6.19*	240 to < 300 *6.19 to < 7.77*	≥ 300 *≥ 7.77*	NA
< 18 years of age	170 to < 200 *4.40 to < 5.15*	200 to < 300 *5.15 to < 7.77*	≥ 300 ≥ *7.77*	NA
LDL, Fasting, High ≥ 18 years of age	130 to < 160 *3.37 to < 4.12*	160 to < 190 *4.12 to < 4.90*	≥ 190 ≥ *4.90*	NA

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
> 2 to < 18 years of age	110 to < 130 *2.85 to < 3.34*	130 to < 190 *3.34 to < 4.90*	≥ 190 ≥ *4.90*	NA
Triglycerides, Fasting, High	150 to 300 *1.71 to 3.42*	>300 to 500 *>3.42 to 5.7*	>500 to < 1,000 *>5.7 to 11.4*	> 1,000 *> 11.4*
Magnesium[16], Low (mEq/L; *mmol/L*)	1.2 to < 1.4 *0.60 to < 0.70*	0.9 to < 1.2 *0.45 to < 0.60*	0.6 to < 0.9 *0.30 to < 0.45*	< 0.6 *< 0.30*
Phosphate, Low (mg/dL; *mmol/L*) > 14 years of age	2.0 to < LLN *0.81 to < LLN*	1.4 to < 2.0 *0.65 to < 0.81*	1.0 to < 1.4 *0.32 to < 0.65*	< 1.0 *< 0.32*
1 to 14 years of age	3.0 to < 3.5 *0.97 to < 1.13*	2.5 to < 3.0 *0.81 to < 0.97*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
< 1 year of age	3.5 to < 4.5 *1.13 to < 1.45*	2.5 to < 3.5 *0.81 to < 1.13*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
Potassium, High (mEq/L; *mmol/L*)	5.6 to < 6.0 *5.6 to < 6.0*	6.0 to < 6.5 *6.0 to < 6.5*	6.5 to < 7.0 *6.5 to < 7.0*	≥ 7.0 *≥ 7.0*
Potassium, Low (mEq/L; *mmol/L*)	3.0 to < 3.4 *3.0 to < 3.4*	2.5 to < 3.0 *2.5 to < 3.0*	2.0 to < 2.5 *2.0 to < 2.5*	< 2.0 *< 2.0*
Sodium, High (mEq/L; *mmol/L*)	146 to < 150 *146 to < 150*	150 to < 154 *150 to < 154*	154 to < 160 *154 to < 160*	≥ 160 *≥ 160*
Sodium, Low (mEq/L; *mmol/L*)	130 to < 135 *130 to < 135*	125 to < 130 *125 to < 135*	121 to < 125 *121 to < 125*	≤ 120 *≤ 120*
Uric Acid, High (mg/dL; *mmol/L*)	7.5 to < 10.0 *0.45 to < 0.59*	10.0 to < 12.0 *0.59 to < 0.71*	12.0 to < 15.0 *0.71 to < 0.89*	≥ 15.0 *≥ 0.89*
HEMATOLOGY				
Absolute CD4+ Count, Low (cell/mm^3; *cells/L*) > 5 years of age (not HIV infected)	300 to < 400 *300 to < 400*	200 to < 300 *200 to < 300*	100 to < 200 *100 to < 200*	< 100 *< 100*
Absolute Lymphocyte Count, Low (cell/mm^3; *cells/L*) > 5 years of age (not HIV infected)	600 to < 650 *0.600 x 10^9 to < 0.650 x 10^9*	500 to < 600 *0.500 x 10^9 to < 0.600 x 10^9*	350 to < 500 *0.350 x 10^9 to < 0.500 x 10^9*	< 350 *< 0.350 x 10^9*

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Absolute Neutrophil Count (ANC), Low (cells/mm^3; *cells/L*) > 7 days of age	800 to 1,000 *0.800 x 10^9 to 1.000 x 10^9*	600 to 799 *0.600 x 10^9 to 0.799 x 10^9*	400 to 599 *0.400 x 10^9 to 0.599 x 10^9*	< 400 *< 0.400 x 10^9*
2 to 7 days of age	1,250 to 1,500 *1.250 x 10^9 to 1.500 x 10^9*	1,000 to 1,249 *1.000 x 10^9 to 1.249 x 10^9*	750 to 999 *0.750 x 10^9 to 0.999 x 10^9*	< 750 *< 0.750 x 10^9*
≤ 1 day of age	4,000 to 5,000 *4.000 x 10^9 to 5.000 x 10^9*	3,000 to 3,999 *3.000 x 10^9 to 3.999 x 10^9*	1,500 to 2,999 *1.500 x 10^9 to 2.999 x 10^9*	< 1,500 *< 1.500 x 10^9*
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to < 200 *1.00 to < 2.00* OR 0.75 to < 1.00 x LLN	75 to < 100 *0.75 to < 1.00* OR ≥ 0.50 to < 0.75 x LLN	50 to < 75 *0.50 to < 0.75* OR 0.25 to < 0.50 x LLN	< 50 *< 0.50* OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin[17], Low (g/dL; *mmol/L*)[18] ≥ 13 years of age (male only)	10.0 to 10.9 *6.19 to 6.76*	9.0 to < 10.0 *5.57 to < 6.19*	7.0 to < 9.0 *4.34 to < 5.57*	< 7.0 *< 4.34*
≥ 13 years of age (female only)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
57 days of age to < 13 years of age (male and female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
36 to 56 days of age (male and female)	8.5 to 9.6 *5.26 to 5.99*	7.0 to < 8.5 *4.32 to < 5.26*	6.0 to < 7.0 *3.72 to < 4.32*	< 6.0 *< 3.72*
22 to 35 days of age (male and female)	9.5 to 11.0 *5.88 to 6.86*	8.0 to < 9.5 *4.94 to < 5.88*	6.7 to < 8.0 *4.15 to < 4.94*	< 6.7 *< 4.15*
8 to ≤ 21 days of age (male and female)	11.0 to 13.0 *6.81 to 8.10*	9.0 to < 11.0 *5.57 to < 6.81*	8.0 to < 9.0 *4.96 to < 5.57*	< 8.0 *< 4.96*
≤ 7 days of age (male and female)	13.0 to 14.0 *8.05 to 8.72*	10.0 to < 13.0 *6.19 to < 8.05*	9.0 to < 10.0 *5.59 to < 6.19*	< 9.0 *< 5.59*
INR, High (not on anticoagulation therapy)	1.1 to < 1.5 x ULN	1.5 to < 2.0 x ULN	2.0 to < 3.0 x ULN	≥ 3.0 x ULN
Methemoglobin (% hemoglobin)	5.0 to < 10.0%	10.0 to < 15.0%	15.0 to < 20.0%	≥ 20.0%

PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
PTT, High (not on anticoagulation therapy)	1.1 to < 1.66 x ULN	1.66 to < 2.33 x ULN	2.33 to < 3.00 x ULN	≥ 3.00 x ULN
Platelets, Decreased (cells/mm3; *cells/L*)	100,000 to < 124,999 *100.000 x 10^9 to < 124.999 x 10^9*	50,000 to < 100,000 *50.000 x 10^9 to < 100.000 x 10^9*	25,000 to < 50,000 *25.000 x 10^9 to < 50.000 x 10^9*	< 25,000 < *25.000 x 10^9*
PT, High (not on anticoagulation therapy	1.1 to < 1.25 x ULN	1.25 to < 1.50 x ULN	1.50 to < 3.00 x ULN	≥ 3.00 x ULN
WBC, Decreased (cells/mm^3; *cells/L*) > 7 days of age	2,000 to 2,499 *2.000 x 10^9 to 2.499 x 10^9*	1,500 to 1,999 *1.500 x 10^9 to 1.999 x 10^9*	1,000 to 1,499 *1.000 x 109 to 1.499 x 10^9*	< 1,000 < *1.000 x 10^9*
≤ 7 days of age	5,500 to 6,999 *5.500 x 10^9 to 6.999 x 10^9*	4,000 to 5,499 *4.000 x 10^9 to 5.499 x 10^9*	2,500 to 3,999 *2.500 x 10^9 to 3.999 x 10^9*	< 2,500 < *2.500 x 10^9*
URINALYSIS				
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	NA
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to < 10 RBCs per high power field	≥ 10 RBCs per high power field	Gross, with or without clots OR With RBC casts OR Intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA

1. Blood pressure norms for children < 18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents [Pediatrics, 2011].
2. As per Bazett's formula.
3. For pruritus associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).
4. Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.
5. Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.
6. BMD t and z scores can be found in: [Kanis, 2007].
7. Definition: A delivery of a live-born neonate occurring at ≥ 20 to < 37 weeks gestational age.
8. Definition: A clinically recognized pregnancy occurring at < 20 weeks gestational age.
9. Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.
10. For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).
11. Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.
12. WHO reference tables may be accesed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007_bmi_for_age/en/ for participants > 5 to 19 years of age and http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those ≤ 5 years of age.
13. Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.
14. Direct bilirubin > 1.5 mg/dL in a participant < 28 days of age should be graded as grade 2, if < 10% of the total bilirubin.
15. Use the applicable formula (i.e., Cockroft-Gault in mL/min or Schwatrz in mL/min/1.73m2).
16. To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.
17. Male and female sex are defined as sex at birth.
18. The conversion factor used to convert g/dL to mmol/L is 0.6206 and is the most commonly used conversion factor. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using the appropriate conversion factor for the particular laboratory.