TITLE PAGE

Protocol Title: An open-label, single arm study to evaluate the week 48 efficacy and safety of a two-drug regimen of dolutegravir/lamivudine (DTG/3TC) as a fixed dose combination (FDC), in antiretroviral therapy (ART)-naive HIV-1-infected adolescents, ≥12 to <18 years of age who weigh at least 25 kg.

Protocol Number: 205861/Amendment 03

Short Title: An open label, single arm study of the safety and efficacy of DTG/3TC in therapy-naïve HIV-1 infected adolescents.

Compound Number: GSK1349572+GR109714 (GSK3515864)

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

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

Medical Monitor/SAE Contact Information:

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Regulatory Agency Identifying Number(s): US IND 127475

Approval Date: 20-NOV-2020

SPONSOR SIGNATORY

Sherene Shakib Min, MD, MPH PPD of Clinical Development ViiV Healthcare	**Date**

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 3	*20-Nov-2020*	*2017N326062_03*
Amendment 2	*13-Nov-2019*	*2017N326062_02*
Amendment 1	*13-Jun-2018*	*2017N326062_01*
Original Protocol	*04-Apr-2018*	*2017N326062_00*

Amendment 3: 20-NOV-2020

Overall Rationale for the Amendment:

Guidance for the management of decline in renal function was modified to incorporate instruction based on change from baseline in DAIDS AE severity grading (Grades 1- 4) for serum creatinine and eGFR (further clarification of how to determine creatinine and eGFR grade is also provided). These modifications were made to clarify and simplify participant management. It incorporates stepwise instruction, based on severity grade, for confirmatory testing and assessment, and parameters for temporary holding or permanent discontinuation of study treatment. Further specific guidance on additional investigations that may be required and the need for consultation with the study Medical Monitor regarding further follow-up and management has also been incorporated. An existing protocol exclusion criterion excludes participants with creatinine clearance of <50 mL/min/1.73 m^2 and allows for potential enrollment of participants with a baseline Grade 3 creatinine clearance, 51-59 mL/min/1.73 m^2 (DAIDS Table for AE Severity Grading Grade 3 creatinine clearance parameters are <60 to 30 mL/min/1.73 m^2). Therefore, using a change from baseline in severity grading to take action also provides further clarification for participant management.

Section # and Name	Description of Change	Brief Rationale
Medical Monitor/SAE Contact Information	• Contacts updated	• Contacts updated to align with team member changes
Summary Section 1 and 5.2 Number of Participants	• Number of screened subjects increased from approximately 40 to approximately 80	• Update made due to screen fail rate
Section 2 Schedule of Activities	• Corrected typos and updated abbreviations	• To improve quality of the protocol
Section 3.1 Study Rationale	• Included approval of Dovato in multiple countries	• Updated to align with current approvals

Section # and Name	Description of Change	Brief Rationale
Section 3.3.1 Risk Assessment	• Removed reference to TDF and FTC • Removed reported risk associated with the use of TDF in clinical practice • Updated exclusionary language • Updated risk of neural tube defect to reflect current data (change in rate from 0.3% to 0.19). • Clarified how renal function will be monitored	• Risk mitigation strategy related to renal function (Section 3.3.1) was updated to align with changes applied in Section 12.9.1.3 (Decline in Renal Function). • Recent data from surveillance study in Botswana added for completeness.
Section 7.9 Concomitant Therapy	• Added COVID-19 treatment and drug interaction guidance	• Clarified to consult with Study Medical Monitor to evaluate appropriate options and whether study participation remains appropriate.
Section 8.2 Withdrawal from the Study and Stopping Criteria and 12.4.3 Informed Consent and Assent Process	• Added instruction on how to manage participants who have a guardianship status change such that they become a ward of State during the study	• This modification was made to clarify and simplify participant management
Sections 9.3.2, 12.8.6 and 12.10.2 Pregnancy	• Updated pregnancy reporting timeframes from 2 weeks to 24 hours	• To align with current pregnancy notification timelines
Section 9.4 Treatment of Overdose	• Added reference for intentional overdose	• Added a reference to Section 9.3.4 which provides additional instruction
Section 9.6.1.1 Collection of Sparse PK Samples	• Added collection timeframe post previous dose	• Clarified the pre-dose samples should be collected 20-28 hours post previous dose
Section 10.3.4 Other Analyses	• Added special statistical and data analysis may be warranted	• These may be warranted in the event COVID-19, related epidemics or natural disasters that may affect the study

Section # and Name	Description of Change	Brief Rationale
Section 11 References	• Added DTG Investigator's Brochure versions 13 and 14 • Updated references	• Added DTG Investigator's Brochure (IB) version updates for completeness • Updated references to align with amendment modifications for completeness.
Section 12.4.3 Informed Consent and Assent Process	• Added instruction on how to manage participants who have a guardianship status change such that they become a ward of the state during the study	• This modification was made to clarify and simplify participant management
Section 12.7 Appendix 7 Laboratory/Chemistries Table	• Added instruction to use absolute value for creatinine and creatinine clearance to determine severity grade	• For clarity, added reference to Section 12.9.1.3 for details on toxicity management
Section 12.8.7 Appendix Reporting COVID-19 AEs and SAEs	• Added section for reporting COVID-19 AEs and SAEs	• To provide guidance on the reporting of COVID-19 specific AEs and SAEs
Section 12.9 Appendix 9: Toxicity Management	• Added reference for general guidelines on the management of specific toxicities	• For clarity, added cross reference to Section 12.9.1 for general guidelines on the management of specific toxicities
Section 12.9.1.3 Appendix Decline in Renal Function	• Modified to incorporate instruction based on change from baseline in DAIDS AE severity grading (Grades 1- 4) for serum creatinine and eGFR (with further clarification of how to determine creatinine and eGFR grade) and guidance on further investigations/discussions required for appropriate patients and the need for timely confirmatory testing.	• This modification was made to clarify and simplify participant management
Section 12.12 Appendix 12: COVID-19 Guidance	• Added COVID-19 guidance	• This modification was made to provide COVID-19 participant management

Section # and Name	Description of Change	Brief Rationale
Throughout	• Incorporated minor clarifications, updated links and abbreviations and corrected typos	• To improve quality of the protocol

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1. SUMMARY

Protocol Title: An open-label, single arm study to evaluate the week 48 efficacy and safety of a two-drug regimen of dolutegravir/lamivudine (DTG/3TC) as a fixed dose combination (FDC), in antiretroviral therapy (ART)-naive HIV-1-infected adolescents, 12 to <18 years of age who weigh at least 25 kg.

Short Title: An open label, single arm study of the safety and efficacy of DTG/3TC in therapy-naïve HIV-1 infected adolescents.

Rationale: Data from this adolescent trial is intended to supplement datasets from GEMINI-1 and GEMINI-2 studies (204861 and 205543), 2 large, global, randomized, double-blind, active controlled clinical trials of DTG plus 3TC in HIV-1 infected ART-naïve adults. As such, data from this trial will provide 'bridging' information for regulatory authorities and treating clinicians. The dual combination of DTG plus 3TC is under assessment in pediatric participants 2 to <12 years of age in a separate study.

Objectives and Endpoints:

Objective	Endpoint
Primary	
• To assess the antiviral activity of DTG/3TC in antiretroviral naïve HIV-1 infected adolescents.	• The proportion of participants with plasma HIV-1 RNA less than 50 c/mL at Week 48 using the Snapshot algorithm (ITT-E population).
Secondary	
• To assess the early antiviral activity of DTG/3TC and to determine the extended long term (≥96 weeks) safety, tolerability, and viral response of DTG/3TC in antiretroviral naïve HIV-1 infected adolescents.	• Proportion of participants with plasma HIV-1 RNA <200 and <50 copies/mL at Week 24, Week 96 and Week 144. • Proportion of participants with plasma HIV-1 RNA <200 copies/mL at Week 48 • Incidence and severity of AEs and laboratory abnormalities through 144 weeks • Proportion of participants who discontinue treatment due to AEs through 144 weeks • Safety and tolerability assessments at Weeks 96 and 144. • Viral load monitoring after Week 48 through Week 144.

Objective	Endpoint
• To evaluate the effect of DTG/3TC on immunologic response from baseline to 24 and 48 weeks	• Change from baseline in CD4+ and CD8+ cell count and ratio at Week 24 and 48. • Incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome (AIDS), and death) through Weeks 24 and 48.
• To assess the safety and tolerability of DTG/3TC in HIV-1 infected adolescents at 24 and 48 weeks	• Incidence and severity of AEs and laboratory abnormalities through 24 and 48 weeks • Proportion of participants who discontinue treatment due to AEs through 24 and 48 weeks
• To assess DTG and 3TC exposure and to evaluate the steady-state pharmacokinetics of DTG and 3TC in HIV-1 infected adolescents	• Steady-state plasma PK parameters of DTG and 3TC will be assessed using intensive PK collected in a subset of participants.
• To assess development of viral resistance to DTG and 3TC in participants experiencing protocol-defined virologic failure (i.e. meeting confirmed virologic withdrawal criteria).	• Incidence of observed genotypic and phenotypic resistance to DTG and 3TC for participants meeting confirmed virologic withdrawal criteria.

Overall Design: This is an open label, single arm, 48-week assessment of the fixed dose combination of DTG/3TC in HIV-1 infected, antiretroviral naïve adolescents.

Number of Participants: This study will be conducted in approximately 30 HIV-1 infected, treatment naïve adolescent participants with screening plasma HIV-1 RNA ≤500,000 c/mL. Approximately 80 participants will be screened to enable enrolment of approximately 30 participants.

Treatment Groups and Duration: All participants will receive the fixed dose combination of DTG/3TC (50/300 mg) for once daily dosing. After a Screening Period of up to 28 days, all participants will be treated for 48-week Treatment Phase. Participants who successfully complete 48 weeks of therapy and who continue to receive benefit from this two-drug regimen may enter a 96-week study Extension Phase. Participants who successfully complete the Extension Phase and who continue to receive benefit from this two-drug regimen will have access to this regimen in a Continuation Phase until it is available locally.

Analysis: The primary endpoint of the proportions of participants meeting the criteria for virologic success as defined by the US Food and Drug Administration (FDA) snapshot algorithm will be reported with exact Clopper Pearson 95% confidence intervals. Safety analyses will be summarized by visit.

2. SCHEDULE OF ACTIVITIES (SOA)

Procedure	Screening[a]	Treatment Phase (Week)									Extension Phase[b]	Continuation Phase[c]	End Continuation Phase Visit	Withdrawal[d]	Follow Up[e]	Notes
		Baseline/ Day 1	1	4	8	12	16	24	36	48	Every 12 weeks after Week 48 through Week 144	Every 12 weeks after Week 144	.	.	.	
Clinical and Other Assessments																
Written informed consent and assent	SC	.	.	.	.	.	.	.	.	.	.	.	.	.	.	Assent will be obtained as appropriate according to local guidelines. Written informed consent must be obtained from the participant if he/she reaches the age of majority while on study.

[a] **Screening**: Enrolment may occur as soon as all Screening results are available.

[b] **Extension Phase**: All participants who successfully complete treatment through Week 48 will have the opportunity to enter the Extension Phase.

[c] **Continuation Phase**: If required by local regulations, study participants who have successfully completed the study through Week 144 may enter the Continuation Phase, regardless of age, and will continue to receive DTG/3TC until it is available locally (See Section 7.10, Treatment after the End of the Study). Prior to transitioning to locally approved and available supply, the participant will return to complete a final End of Continuation Phase visit.

[d] **Withdrawal**: Participants will complete a Withdrawal visit at the time they withdraw from the study and will return for a follow-up visit 4 weeks after the last dose of study medication.

[e] **Follow-up:** An in-clinic Follow-Up visit will be conducted 4 weeks after the last dose of study medication upon withdrawal from study. A follow-up visit will not be applied for participants completing the End of Continuation Phase Visit, (as they will continue to receive DTG plus 3TC) or for participants who withdraw consent for further participation at the time of early withdrawal from the study.

Procedure	Screening[a]	Treatment Phase (Week)									Extension Phase[b]	Continuation Phase[c]	End Continuation Phase Visit	Withdrawal [d]	Follow Up [e]	Notes
		Baseline/ Day 1	1	4	8	12	16	24	36	48	Every 12 weeks after Week 48 through Week 144	Every 12 weeks after Week 144	.	.	.	
Inclusion and exclusion criteria	SC	B	.	.	.	.	.	.	.	.	.	.	.	.	.	Inclusion/exclusion criteria will be assessed fully at the Screening visit. Changes between the Screening visit and the Day 1 visit should be considered to ensure eligibility, including review of additional assessments performed at Day 1.
Demography	SC	.	.	.	.	.	.	.	.	.	.	.	.	.	.	Including year of birth, sex, race, ethnicity.
Medical history (includes substance abuse)	SC	.	.	.	.	.	.	.	.	.	.	.	.	.	.	Full medical history will be conducted prior to enrollment and include assessments of cardiovascular, metabolic (e.g., Type I or II diabetes mellitus), psychiatric (e.g., depression), renal (e.g., nephrolithiasis, nephropathy, renal failure), and bone disorders.
Prior ART/PMTCT history, as applicable	SC	.	.	.	.	.	.	.	.	.	.	.	.	.	.	
Tanner staging score		B	.	.	.	.	.	.	.	48	E (Every 48 Weeks)	.	.	.	.	Tanner scoring will be collected until the end of adolescence. During the Extension Phase, assess Tanner Score only every 48 weeks.
Concurrent medical conditions	SC	.	.	.	.	.	.	.	.	.	.	.	.	.	.	

Procedure	Screening[a]	Treatment Phase (Week)									Extension Phase[b]	Continuation Phase[c]	End Continuation Phase Visit	Withdrawal [d]	Follow Up [e]	Notes
		Baseline/ Day 1	1	4	8	12	16	24	36	48	Every 12 weeks after Week 48 through Week 144	Every 12 weeks after Week 144	.	.	.	
Vital signs	SC	.	.	.	.	.	.	.	.	.	.	.	.	.	.	
HIV risk factors and mode of transmission	.	B	.	.	.	.	.	.	.	.	.	.	.	.	.	
CDC or WHO HIV-1 classification	SC	B	.	.	.	.	.	.	.	.	.	.	.	.	.	See Section 12.6, Appendix 6: CDC Classification and WHO Staging for HIV-1 Infection
HIV associated conditions	.	.	.	4	8	12	16	24	36	48	E	C	EC	W	.	
Columbia Suicidality Rating Scale	.	B	.	4	8	12	16	24	36	48	E	C	EC	W	.	On Day 1, the electronic Columbia Suicidality Severity Rating Scale eC-SSRS, (patient completed questionnaire) is to be administered prior to enrolment. CSSRS participant level reports should reviewed, signed by Investigator or Sub-Investigator and filed in site source. Actions taken for positive findings should be clearly documented.
Concomitant medication	SC	B	.	4	8	12	16	24	36	48	E	C	EC	W	F	
Symptom directed physical examination/Medical decision-making including height and weight	SC	B	.	4	8	12	16	24	36	48	E	.		W	F	

Procedure	Screening[a]	Treatment Phase (Week)									Extension Phase[b]	Continuation Phase[c]	End Continuation Phase Visit	Withdrawal [d]	Follow Up [e]	Notes
		Baseline/ Day 1	1	4	8	12	16	24	36	48	Every 12 weeks after Week 48 through Week 144	Every 12 weeks after Week 144	.	.	.	
12-lead ECG	SC	.	.	.	.	.	.	.	.	.	.	.	.	.	.	Perform 12-lead ECG after resting in a semi-supine position for at least 5 minutes.
Adverse events	SC	B		4	8	12	16	24	36	48	E	C	EC	W	F	Only SAEs related to study participation or to a concomitantly administered ViiV Healthcare/GlaxoSmithKline (GSK) product will be collected between obtaining informed consent and administration of study drug at Day 1.
Serious adverse events	SC	B		4	8	12	16	24	36	48	E	C	EC	W	F	
Laboratory Assessments																Sites should make every effort to ship lab samples to Q2 on the same day as sample collection.
Plasma for HIV genotyping	SC	.	.	.	.	.	.	.	.	.	.	.	.	.	.	
Quantitative plasma HIV-1 RNA	SC	B	.	4	8	12	16	24	36	48	E	C	EC	W	.	
Lymphocyte subsets	SC	B	.	4	8	12	16	24	36	48	E	.	.	W	.	

Procedure	Screening[a]	Treatment Phase (Week)									Extension Phase[b]	Continuation Phase[c]	End Continuation Phase Visit	Withdrawal [d]	Follow Up [e]	Notes
		Baseline/ Day 1	1	4	8	12	16	24	36	48	Every 12 weeks after Week 48 through Week 144	Every 12 weeks after Week 144	.	.	.	
Plasma for storage	SC	B	.	4	8	12	16	24	36	48	E	C	EC	W	.	Plasma samples for storage will be collected at each visit starting at Screening, including any unscheduled visits. These samples will be used when needed such as when samples are lost, arrive at the laboratory unevaluable, or for PK or genotypic and/or phenotypic analyses when participants meet Suspected and Confirmed Virologic Withdrawal criteria.
Clinical chemistry	SC	B	.	4	8	12	16	24	36	48	E	.	.	W	F	
Hematology	SC	B	.	4	8	12	16	24	36	48	E	.	.	W	F	
PT/INR	SC	.	.	.	.	.	.	.	.	.	.	.	.	.	.	
Fasting lipids, glucose, HbA1c	.	B	.	.	.	.	.	24		48	E	.	.	W	.	An overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable. During Extension Phase, collect fasting lipids, glucose, and glycated haemoglobin (Hb1Ac) only every 24 weeks. Collect at Withdrawal only if withdrawal visit occurs at Weeks 48,96 or 144
Urinalysis and spot urine for protein analysis	.	B	.	.	.	12	.	24	.	48	E	.	.	W	F	A morning specimen is preferred

Procedure	Screening[a]	Treatment Phase (Week)									Extension Phase[b]	Continuation Phase[c]	End Continuation Phase Visit	Withdrawal [d]	Follow Up [e]	Notes
		Baseline/ Day 1	1	4	8	12	16	24	36	48	Every 12 weeks after Week 48 through Week 144	Every 12 weeks after Week 144	.	.	.	
Pregnancy test	SC (S)	B (U)	.	4 (S)	8 (S)	12 (S)	16 (S)	24 (S)	36 (S)	48 (S)	E (S)	C (S)	EC (S)	W (S)	.	Pregnancy testing will be conducted (females of reproductive potential only) on serum (S) samples with the exception of Day 1, which must be a urine (U) test to confirm status prior to administration of study treatment. Remind females of reproductive potential of the need to avoid pregnancy while in study and adherence to the study's contraception requirements.
HBsAg, anti-HBc, anti-HBs, and HBV DNA	SC	.	.	.	.	.	.	.	.	.	.	.	.	.	.	HBV DNA testing will be performed for participants with positive anti-HBc and negative HBsAg and negative anti-HBs (past and/or current evidence). Participants will have to return to the clinic to provide a sample for HBV DNA testing prior to enrollment.
HCV antibody	SC	.	.	.	.	.	.	.	.	.	.	.	.	.	.	
RPR	SC	.	.	.	.	.	.	.	.	.	.	.	.	.	.	
Sample for Ctrough measurement	.	.	.	.	8	.	16	.	36	48	.	.	.	.	.	

Procedure	Screening[a]	Treatment Phase (Week)								Extension Phase[b]	Continuation Phase[c]	End Continuation Phase Visit	Withdrawal [d]	Follow Up [e]	Notes
		Baseline/ Day 1	1	4	8	12	16	24	36	48	Every 12 weeks after Week 48 through Week 144	Every 12 weeks after Week 144	.	.	.	
Sample for pharmacokinetic analysis (sparse collection – all participants)	.	.	.	4	.	12	.	24	.	.	.	.	.	.	.	At each scheduled visit, collect a pre-dose sample and a post dose sample as described in Section 9.6.1
Dispense PK Diary Card	.	B	.	4	8	12	16	24	36	48	.	.	.	.	.	Participant to complete dosing diary for 3 days prior to PK and Ctrough sampling visits. The PK visit should be re-scheduled if the participant took their morning dose prior to coming into the clinic on the sparse or intensive PK sampling day.
Sample for pharmacokinetic analysis (intensive serial collection – subset of participants)	.	.	1	.	.	.	.	.	.	.	.	.	.	.	.	To be collected in a subset of participants between Days 5 and 10. Samples will be drawn between days 5 and 10 at the following timepoints: pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6,10, and 24 hours post dose. See Section 9.6.2.3
Dispense Intensive PK Diary Card to Intensive PK sub-set	.	B	.	.	.	.	.	.	.	.	.	.	.	.	.	Participant to complete dosing diary for 3 days prior to PK sampling visit. The PK visit should be re-scheduled if the participant took their morning dose prior to coming into the clinic on the intensive PK sampling day.

Procedure	Screening[a]	Treatment Phase (Week)									Extension Phase[b]	Continuation Phase[c]	End Continuation Phase Visit	Withdrawal [d]	Follow Up [e]	Notes
		Baseline/ Day 1	1	4	8	12	16	24	36	48	Every 12 weeks after Week 48 through Week 144	Every 12 weeks after Week 144	.	.	.	
Whole blood sample (virology)	.	B	.	.	.	.	.	.	.	48	E (at Week 144)	.	.	W	F	Whole blood (Virology) may be used for virologic analyses as described in the protocol. In the Extension Phase, collect only at Week 144.
Study Treatment																
IVRS/IWRS	SC	B	1	4	8	12	16	24	36	48	E	C	EC	W	F	
Dispense study medication	.	B	.	4	8	12	16	24	36	48	E	C	.	.	.	Medication may be dispensed until the participant's last on study visit.
Study medication accountability	.	.	.	4	8	12	16	24	36	48	E	C	EC	W	.	

anti-HBc = antibody to hepatitis B core antigen, anti-HBs = hepatitis B surface antibody, ART = antiretroviral therapy, B= Baseline, C= Continuation Phase, CDC = Centers for Disease Control and Prevention, DNA = deoxyribonucleic acid, E = Extension Phase Visit, EC= End of Continuation Phase Visit, ECG = electrocardiograph, F= Follow-up Visit, HBsAg = hepatitis B surface antigen, HCV = hepatitis C virus, HIV-1 = human immunodeficiency virus type 1, INR = international normalized ratio, IVRS = interactive voice recognition system, IWRS = interactive web recognition system, PMTCT = prevention of mother to child transmission, RNA = ribonucleic acid, RPR = rapid plasma regain, SC= Screening, W= Withdrawal Visit

3. INTRODUCTION

3.1. Study Rationale

Current HIV treatment guidelines recommend first-line antiretroviral (ARV) regimens consisting of two nucleoside/nucleotide analogue reverse transcriptase inhibitors (NRTIs) as a "backbone" combined with a third agent from the non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (ritonavir-boosted) (PI/RTV), or integrase strand transfer inhibitor (INSTI) classes [DHHS, 2019; EACS, 2020; International Antiviral Society -USA, 2018]. These regimens are highly efficacious and generally well tolerated. However, because these regimens need to be taken life-long, there is growing concern about long-term toxicities thus there is great interest from patients and clinicians in unique regimens that might avoid such toxicities by minimizing the number of antiretrovirals without sacrificing long-term antiviral efficacy.

DTG is a potent dual cation binding INSTI, exhibiting rapid reduction in viral load, best in class efficacy, and a high barrier to resistance. In addition, due to its mechanism of metabolism, DTG lacks many of the frequent drug interactions associated with other medications commonly taken by HIV-positive patients. To date, the efficacy, pharmacokinetics (PK), safety and drug interaction potential of DTG has been evaluated in an extensive program of Phase I to IIIB clinical trials [TIVICAY Package Insert, 2020; DTG Investigators Brochure GlaxoSmithKline Document Number RM2007/00683/12].

3TC is a potent cytidine nucleoside analogue without major side effects and has a well proven safety profile. Available since 1995 as a single agent [EPIVIR™ Package Insert, 2020], it is also available as part of the FDC products COMBIVIR (zidovudine (ZDV)/3TC), TRIZIVIR (abacavir (ABC)/ZDV/3TC), EPZICOM/KIVEXA (ABC/3TC) and TRIUMEQ (DTG/ABC/3TC). 3TC monotherapy is known to select for resistance due to a single point mutation that reduces antiviral activity. However, it is predicted that 3TC, when combined with DTG with its high barrier to resistance and ability to confer a very rapid decline in HIV-1 RNA, may be less likely to select for resistance consistent with clinical studies combining DTG, 3TC and ABC [DTG Investigators Brochure GlaxoSmithKline Document Number RM2007/00683/12; Walmsley, 2013].

DTG plus 3TC FDC (50/300 mg) is marketed as DOVATO and approved in the United States, Canada, Europe and multiple other markets. DTG plus 3TC provides a novel, well-tolerated two-drug first-line regimen for HIV-infected treatment- naïve patients, limiting the risk of many common adverse reactions associated with other ARV drugs. This regimen is particularly valuable for patients with co-morbid conditions such as bone or cardiovascular disease, and in resource-limited settings due to DTG's known efficacy advantages and both drugs' tolerability and long-term safety profiles, as well as ease of use (once daily dosing, no food dosing effects/requirements, and limited potential for drug-drug interactions).

The combination of DTG plus 3TC is under investigation in 2 large, randomized, double-blind, active controlled clinical trials in adult participants (GEMINI-1 and GEMINI-2 Studies 204861 and 205543). GEMINI 1 and GEMINI 2 showed that in adult HIV-1 infected ART-naïve participants with a Screening HIV-1 RNA of ≥500,000 copies/mL

(c/mL) and with no drug-resistance mutations, DTG + 3TC was non-inferior to DTG + tenofovir disoproxil fumarate/ emtricitabine (TDF/FTC) at Week 48 [Cahn, 2019]. The proportion of participants with plasma HIV-1 RNA <50 c/mL was similar in each treatment group. At least 90% of participants in each treatment group had plasma HIV-1 RNA <50 c/mL using the Snapshot algorithm. DTG + 3TC was effective across a diverse spectrum of ART-naïve participants, including those with high Baseline HIV-1 RNA (>100,000 c/mL). DTG plus 3TC continued to offer non-inferior efficacy to DTG plus TDF/FTC at Week 96 [Cahn, 2019]. A pooled analysis of the two studies at Week 96 showed that 86% (616/716) in the DTG + 3TC arm had HIV-1 RNA <50 copies per millilitre (c/mL) compared with 90% (642/717) in the DTG plus TDF/FTC arm [adjusted difference -3.4 (-6.7,0.0)] [Cahn, 2019]. Across both studies, 11 participants (1.5%) on DTG plus 3TC and seven (1.0%) on DTG plus TDF/FTC met protocol-defined virologic withdrawal criteria through to Week 96. No patient who experienced confirmed virologic withdrawal in either treatment arm developed treatment-emergent resistance. The safety results for DTG plus 3TC were consistent with the product labelling for the medicines. No patient who experienced virologic failure in either treatment arm developed treatment-emergent resistance.

Data from this adolescent trial is intended to supplement the dataset in adults. As such, this trial will provide 'bridging' information for regulatory authorities and treating clinicians (CDER, 2015). The dual combination of DTG plus 3TC will be assessed in pediatric participants 2 to <12 years of age in a separate study.

3.2. Background

A number of clinical studies have reported supportive clinical data on the efficacy as well as favorable safety of two-drug treatment regimens as either initial therapy or as switch therapy in virologically suppressed patients, when they include a highly-effective ARV, such as a boosted PI or an INSTI.

One of the potential risks of a two-drug regimen, such as DTG plus 3TC, is the increase in virologic failure associated with the emergence of resistance. DTG, with its higher barrier to resistance, may reduce treatment-emergent resistance in patients taking a two-drug regimen. The overall efficacy data from the pivotal Phase III studies of DTG in ART-naïve participants are extensive, with no resistance mutations being identified through 144 weeks of treatment (SINGLE, ING114467) [Walmsley, 2015]. The absence of treatment-emergent mutations to DTG or background agents in ART-naïve individuals, rapid virologic response demonstrated for DTG-based regimens, and the *in vitro* potency and well-tolerated safety profile of both DTG and 3TC all provide a strong rationale for the development of a DTG/3TC single tablet regimen (STR) as a treatment option for patients. In the Gemini studies, there was no emergent INSTI or NRTI resistance observed for participants meeting confirmed virologic withdrawal criterion in either the DTG + 3TC or DTG + TDF/FTC treatment arms [Cahn, 2019].

Two-drug regimens in HIV-1 infected, antiretroviral treatment-naïve patients.

Three randomized clinical trials have shown comparable results of PI/RTV-based dual therapies among treatment-naïve patients:

- The AIDS Clinical Trials Group Study A5142 found that the virological efficacy of an NRTI-sparing regimen of efavirenz (EFV) plus lopinavir/ritonavir (LPV/RTV) was similar to that of the EFV plus two NRTIs but was more likely to be associated with drug resistance [Riddler, 2008].
- In the PROGRESS study, patients were randomly assigned to an NRTI-sparing regimen of LPV/RTV plus raltegravir (RAL) or a standard triple-therapy regimen consisting of LPV/RTV plus TDF/FTC FDC [Reynes, 2011]. At 48 weeks, 83.2% of participants in the LPV/RTV plus RAL group and 84.6% of those in the LPV/RTV plus TDF/FTC group achieved plasma viral loads of <50 c/mL, although this study did not enroll patients with advanced HIV disease. The mean baseline HIV-1 RNA was low (~18,000 c/mL).
- The GARDEL (Global AntiRetroviral Design Encompassing Lopinavir/r and Lamivudine vs LPV/r based standard therapy) study randomly assigned 426 treatment-naïve patients with HIV to receive open-label LPV/RTV (400 mg/100 mg) twice daily plus two NRTIs (triple therapy) or an experimental dual therapy regimen of LPV/RTV plus 3TC (150 mg) twice daily [Butler, 2017].
- [Cahn, 2014]. After 48 weeks of treatment, the virological response rates were 88.3% in the dual-therapy group and 83.7% in the triple-therapy group, meeting the study's primary non-inferiority endpoint. All enrolled participants who maintained viral suppression at Week 48 were invited to participate in an extension phase up to Week 96; non-inferiority was again demonstrated with response rates at Week 96 of 90.3% (dual therapy) and 84.4% (triple-therapy) [Cahn, 2015].

In addition, two pilot studies supported the concept of a DTG + 3TC two-drug initial regimen.

- The PADDLE trial assessed DTG (50 mg once daily) + 3TC (300 mg once daily) as initial therapy in 20 HIV treatment-naïve participants with no genotypic resistance to 3TC and a viral load of ≤100,000 c/mL at Screening. Participants were enrolled in two separate groups of 10, allowing close evaluation of response while employing a set of stopping rules with intensive follow-up in each cohort. At Week 96, all 18 of the 20 participants who completed the study had undetectable plasma HIV-1 RNA (<50 c/mL). Two participants discontinued treatment early; 1 due to virologic failure at Week 48 and 1 due to a SAE (also at Week 48) [Figueroa, 2017].
- ACTG5353 [Taiwo, 2017] enrolled 120 study participants into the pilot study assessing DTG (50 mg once daily) + 3TC (300 mg once daily) as initial therapy. Participants in this trial had no history or major NRTI, INSTI, nor PI mutations (INSTI resistance testing was performed at Screening) and had plasma HIV-1 RNA between 1000 and 500,000 c/mL. At Week 24, 90% of participants had plasma HIV-1 RNA <50 c/mL. Three participants had plasma HIV-1 RNA ≥50 c/mL. Four participants discontinued study prior to Week 24 (2 moved location, 1 was

incarcerated, 1 was lost to follow up) and three participants discontinued treatment (1 due to pregnancy, 1 for non-compliance and 1 was unable to attend clinic).

Immunologic responses in both of these trials were positive with increases in CD4+ cell counts.

Finally, data from the DOLUAM study [Reynes, 2017] supported the concept of DTG + 3TC as a switch regimen in maintain virologic suppression in participants with plasma HIV-1 RNA <50 c/mL for at least 12 months. In 27 heavily experiences subjects with tolerability issues, there we no reported cases of virologic failure. Two subjects discontinued study early due to AE and one subjects experience a viral 'blip' and wanted to intensify the antiretroviral regimen.

3.3. Benefit/Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with DTG and 3TC can be found in the most recent version of the DTG Investigator's Brochure (IB) and any IB supplements and DTG, 3TC and DOVATO product labels. The following section outlines the risk assessment and mitigation strategy primarily for DTG in this protocol.

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [DTG/3TC] Refer to DTG IB and country product labels for lamivudine for additional information		
DTG: Hypersensitivity reaction (HSR) and rash	HSR has been observed uncommonly with DTG. Rash was commonly reported in DTG Phase IIb/III clinical trials; episodes were generally mild to moderate in intensity; no episodes of severe rash, such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and erythema multiforme were reported.	Participants with history of allergy/sensitivity to any of the study drugs are excluded (Section 6.2). Specific/detailed toxicity management guidance is provided for HSR (Section 12.9.1.4) and rash (Section 12.9.1.5). The participant informed consent form includes information on this risk and the actions participants should take in the event of 1) an HSR or associated signs and symptoms, or 2) developing any type of rash or skin abnormality. For Grade 3/4 rash, except where the aetiology is clear and not associated with study drug or where there is a definitive diagnosis clearly attributable to a concomitant medication (and not to study drug) or to a concomitant infection, participants must permanently discontinue study drug and be withdrawn from the study.
DTG: Drug induced liver injury (DILI) and other clinically significant liver chemistry elevations 3TC: Use in HBV co-infected patients and emergence of HBV variants resistant to 3TC	DTG: Non-clinical data suggested a possible, albeit low, risk for hepatobiliary toxicity with DTG. Drug-related hepatitis is considered an uncommon risk for ART containing DTG regardless of dose or treatment population. For participants with hepatitis B virus (HBV) and/or hepatitis C virus (HCV) co-infection, improvements in immunosuppression as a result of HIV virologic and immunologic responses to DTG-containing ART, along with inadequate therapy for HBV co-infected participants, likely contributed to significant elevations in liver chemistries. A review of postmarketing data found that the number of cases reporting particularly severe liver dysfunction was found to be very low in the context of exposure to DTG and DTG/ABC/3TC. The reported cases of severe liver dysfunction (including acute hepatic failure) are complex with potential confounding factors but in a very small number of cases, drug-	Participants meeting either of the following criteria during the screening period are excluded from participating (Section 6.2). • Alanine aminotransferase (ALT) ≥5 times the upper limit of normal (ULN) or ALT ≥3x ULN and bilirubin ≥1.5x ULN (with >35% direct bilirubin); • Participants positive for Hepatitis B surface antigen (HBsAg); participants negative for HBsAg and negative for Hepatitis B surface antibody (anti-HBs or HBsAb) but positive for Hepatitis B core antibody (anti-HBc) and positive for HBV DNA; • Participants with an anticipated need for any HCV therapy during the first 48 weeks of the study and for HCV therapy based on interferon or any drugs that have a potential for adverse drug:drug interactions with study treatment throughout the entire study period.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	induced liver injury is likely and the role of DTG containing regimens cannot be ruled out particularly in those involving DTG with ABC/3TC or DTG/ABC/3TC. 3TC: Current treatment guidelines [DHHS, 2019; EACS, 2020] do not recommend monotherapy with 3TC for patients with HBV infection, which is what participants enrolled to DTG plus 3TC, would effectively be receiving. Emergence of HBV variants associated with resistance to 3TC has been reported in HIV-1-infected patients who have received 3TC-containing antiretroviral regimens in the presence of concurrent infection with HBV. Additionally, discontinuation of 3TC in HBV co-infected participants can result in severe exacerbations of hepatitis B.	Specific/detailed liver stopping criteria and toxicity management guidance is provided for suspected DILI or other clinically significant liver chemistry elevations (Section 12.3 and Section 12.9.1.1).
DTG: Psychiatric disorders	Psychiatric disorders including suicidal ideation and behaviors are common in HIV-infected patients. Events of suicidal ideation, attempt, behavior and completion were observed in clinical studies of DTG, primarily in participants with a pre-existing history of depression or other psychiatric illness. The events respond rapidly to withdrawal of DTG, or appropriate drug therapy and psychiatric support. The psychiatric profile for DTG (including suicidality, depression, bipolar and hypomania, anxiety and abnormal dreams) was similar to RAL- or favorable compared with EFV-based regimens. The reporting rate for insomnia was statistically higher for blinded DTG plus ABC/3TC compared to EFV/TDF/FTC in ING114467; however, this was not duplicated in any other Phase IIb/III study conducted with DTG.	Participants who in the investigator's judgment, pose a significant suicidality risk, are excluded from participating (Section 6.2). Because of the elevated risk in the HIV- infected population, treatment emergent assessment of suicidality will be monitored during this study. Investigators are advised to consider mental health consultation or referral for participants who experience signs of suicidal ideation or behaviour (Section 9.3.4). The participant informed consent form includes information on this risk of depression and suicidal ideation and behaviours.
DTG and 3TC: Increased rates of virologic failure/ observed resistance	Lower responses in participants with higher baseline viral loads have been observed in previous treatment-naïve studies, including studies with 2-drug arms such as the MODERN study [Stellbrink, 2014].	Participants with evidence of primary viral resistance based on the presence of any major resistance-associated mutation (including M184V) are excluded from this study (Section 6.2).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	DTG, with its higher barrier to resistance, may reduce treatment-emergent resistance in patients taking a two-drug regimen. Week 96 and Week 144 analyses for the Phase III/IIIb clinical studies demonstrate robust maintenance of viral suppression with no finding of HIV-1 resistance in treatment-naïve participants. 3TC: M184V is a common single mutation that leads to full resistance to 3TC.	The study initially will enroll participants with a Screening HIV 1 RNA of 1000 to ≤500,000 c/mL. Participants will have HIV-1 RNA measured at each study visit. An Independent data monitoring committee (IDMC) will be instituted to ensure external objective medical and/or statistical review of efficacy and safety (Section 12.4.5). An ad-hoc review of data by the IDMC will be triggered whenever the number of CVWs exceeds thresholds pre-specified in the IDMC charter (Section 12.4.5).
DTG: Theoretical serious drug interaction with dofetilide, pilsicainide and fampridine (also known as dalfampridine)	Co-administration of DTG may increase dofetilide/pilsicainide/fampridine plasma concentration via inhibition of organic cation transporter 2 (OCT2), resulting in potentially life-threatening toxicity.	The co-administration of DTG with dofetilide, pilsicainide or fampridine is prohibited in the study (Section 7.9.2).
DTG, 3TC: Renal function	Mild elevations of creatinine have been observed with DTG which are related to a likely benign effect on creatinine secretion with blockade of OCT2. DTG has been shown to have no significant effect on glomerular filtration rate (GFR) or effective renal plasma flow. 3TC, is eliminated by renal excretion and exposures increase in patients with renal dysfunction	Participants with a creatinine clearance (CrCL) <50 mL/min/1.73 m^2 are excluded (Section 6.2). CrCl is calculated in all patients prior to initiating therapy, and renal function (CrCl, serum electrolytes) will continue to be monitored at all subsequent study visits. Other measures of renal function, such as urine protein and urine creatinine, will be measured at regular, less frequent intervals throughout. Specific/detailed toxicity management guidance is provided for participants who develop a decline in renal function (Section 12.9.1.3).
DTG: Rhabdomyolysis and Creatine Phosphokinase (CPK) elevations	Grade 3 to 4 CPK elevations have been observed with DTG. Creatine phosphokinase (CPK) elevations were mainly in association with exercise and asymptomatic. No increased risk for clinically significant or serious musculoskeletal disorders such as rhabdomyolysis have been	Specific detailed toxicity management guidance is provided for participants who develop Grade 3 to 4 CPK elevations (Section 12.9.1.7).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	identified for DTG with longer exposure. However, as rhabdomyolysis and myositis are labelled for RAL this is therefore considered a potential risk for DTG.	
DTG: Neural tube defects 3TC:	In a birth outcome surveillance study in Botswana, a numerically higher rate of neural tube defects was reported with exposure to DTG compared to non-dolutegravir containing antiretroviral regimens at the time of conception, however, the difference was not statistically significant. Seven cases of neural tube defects were reported in 3,591 deliveries (0.19%) to mothers taking DTG-containing regimens at the time of conception, compared with 21 cases in 19,361 deliveries (0.11%) to mothers taking non-DTG containing regimens at the time of conception (Prevalence Difference 0.09%; 95% CI -0.03-0.30). In the same study, no increased risk of neural tube defects was reported in women who started DTG during pregnancy. Two out of 4,448 deliveries (0.04%) to mothers who started DTG during pregnancy had a neural tube defect, compared with 5 out of 6,748 deliveries (0.07%) to mothers who started non-DTG-containing regimens during pregnancy. Available data from the Antiretroviral Pregnancy Registry show no difference in the risk of overall major birth defects for lamivudine compared with the background rate for major birth defects of 2.7% in the US reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). Lamivudine produced embryonic toxicity in rabbits at a dose that produced similar human exposures as the recommended clinical dose. The relevance of animal findings to human pregnancy registry data is not known.	Females of childbearing potential are required to have a negative pregnancy test at both Screening and Day 1 of the study. 1. A female subject is eligible to participate if she is not pregnant, not lactating, and, if she is a female of reproductive potential, agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see Appendix 10, Section 12.10.1) from 28 days prior to the first dose of study medication and until the last dose of study medication and completion of the Follow-up visit. 2. Women who are breastfeeding or plan to become pregnant or breastfeed during the study are excluded; 3. Women who become pregnant, or who desire to be pregnant while in the study will have study treatment discontinued and withdrawn from the study. 4. Females of reproductive potential are reminded re: pregnancy avoidance and adherence to contraception requirements at every study visit. 5. Pregnancy status is monitored at every study visit

3.3.2. Benefit Assessment

DTG is conveniently dosed once daily, without need for a PK booster, and with limited safety implications resulting from theoretical or actual drug:drug interactions compared to other ARV agents. DTG and 3TC in combination with other ARVs has demonstrated durable virologic and immunologic response. In addition, the high barrier to resistance observed with DTG should help protect against the development of resistance to both components of the DTG plus 3TC regimen.

Two-drug regimens have been tested in a number of clinical trials (see Section 3.2). Results from these trials paved the way for the exploration of other dual-therapy strategies. DTG plus 3TC, a regimen of two well-characterized antiretrovirals, provides a novel, well-tolerated two-drug regimen for HIV-infected patients, limiting the risk of many common adverse reactions associated with other ARV drugs. Dual therapy also has the potential benefit of decreasing the likelihood of drug-drug interactions and preserving future treatment options by limiting drug exposure.

Study participants may also benefit from the medical tests and screening procedures performed as part of the study.

3.3.3. Overall Benefit:Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with DTG/3TC are justified by the anticipated benefits that may be afforded to HIV-1 infected treatment-naïve adolescents starting this two-drug first-line regimen.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To assess the antiviral activity of DTG/3TC in antiretroviral naïve HIV-1 infected adolescents.	• The proportion of participants with plasma HIV-1 RNA less than 50 c/mL at Week 48 using the Snapshot algorithm (ITT-E population).
Secondary	
• To assess the early antiviral activity of DTG/3TC and to determine the extended long term (≥48 weeks) safety, tolerability, and viral response of DTG/3TC in antiretroviral naïve HIV-1 infected adolescents.	• Proportion of participants with plasma HIV-1 RNA <200 and <50 copies/mL at Week 24, Week 96 and Week 144. • Proportion of participants with plasma HIV-1 RNA <200 copies/mL at Week 48

Objectives	Endpoints
	• Incidence and severity of AEs and laboratory abnormalities through 144 weeks • Proportion of participants who discontinue treatment due to AEs through 144 weeks • Safety and tolerability assessments at Weeks 96 and 144. • Viral load monitoring after Week 48 through Week 144.
• To evaluate the effect of DTG/3TC on immunologic response from baseline to 24 and 48 weeks.	• Change from baseline in CD4+ and CD8+ cell count and ratio at Week 24 and 48. • Incidence of disease progression (HIV-associated conditions, AIDS, and death) through Weeks 24 and 48.
• To assess the safety and tolerability of DTG/3TC in HIV-1 infected adolescents at 24 and 48 weeks.	• Incidence and severity of AEs and laboratory abnormalities through 24 and 48 weeks. • Proportion of participants who discontinue treatment due to AEs through 24 and 48 weeks.
• To assess DTG and 3TC exposure and to evaluate the steady-state pharmacokinetics of DTG and 3TC in HIV-1 infected adolescents.	• Steady-state plasma PK parameters of DTG and 3TC will be assessed using intensive PK collected in a subset of participants
• To assess development of viral resistance to DTG and 3TC in participants experiencing protocol-defined virologic failure (i.e. meeting confirmed virologic withdrawal criteria).	• Incidence of observed genotypic and phenotypic resistance to DTG and 3TC for participants meeting confirmed virologic withdrawal criteria.

All virologic endpoints will be determined in a central laboratory.

5. STUDY DESIGN

5.1. Overall Design

This is a Phase IIIb, single-arm, open-label, multi-center assessment of DTG/3TC in approximately 30 HIV-1 infected, treatment-naive adolescents with plasma HIV-1 RNA between 1,000 and ≤500,000 c/mL. All enrolled participants will receive an open-label, two-drug regimen of DTG/3TC for 48 weeks. Participants who successfully complete 48 weeks of treatment may enter the study Extension Phase for an additional 96 weeks. At

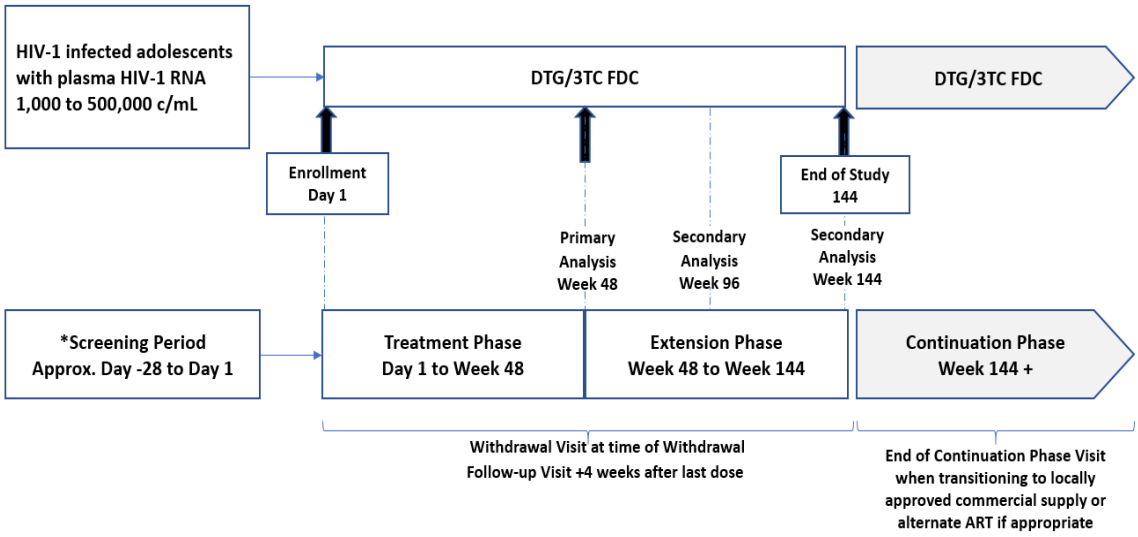
the end of the study, participants who continue to receive benefit from DTG/3TC and for whom these medications are not locally accessible, will have access to medication in a Continuation Phase until it is available locally (See Section 7.10).

Data from this study will be used to assess the safety, efficacy and tolerability of this combination of DTG/3TC in adolescents relative to what is observed in large and controlled clinical studies being conducted in adults.

The study will comprise:

- Screening Phase (approximately Day -28 to Day 1)
- Treatment Phase (Day 1 to Week 48)
- Extension Phase (Week 48 to Week 144)
- Continuation Phase (After Week 144; See Section 7.10)

Figure 1 205861 Study Schematic



* Retesting of an exclusionary lab result (except for exclusionary HIV-1 resistance), is allowed during the screening window (does not require re-screening). In cases of central laboratory assay failure or shipment failure, the screening period may be extended to 35 days to accommodate sample analysis and reporting. Approval of the Medical Monitor is required.

5.2. Number of Participants

Approximately 80 participants will be screened to achieve 30 enrolled participants. See Section 10.1 for sample size determination details.

Participants who prematurely discontinue the study will not be replaced.

A subset of approximately 12 participants will provide intensive PK samples to ensure data are available from at least 10 evaluable participants.

5.3. Participant and Study Completion

A participant will be considered evaluable for the primary endpoint if he/she is successfully treated exclusively with DTG/3TC and has completed 48 weeks of treatment or is classified as a treatment failure (met any withdrawal criteria).

A participant will be considered to have completed treatment if he/she completes the Week 48 study visit while still taking DTG/3TC.

A participant will be considered to have completed the study if he/she completes 48 weeks of treatment and either completes the follow up visit or continues into the Extension Phase of this study.

A participant will be considered to have completed the Extension Phase if he/she completes the Week 144 visit.

A participant will be considered to have completed the Continuation Phase after completion of the End of Continuation Phase Visit.

The end of the study will occur after the last participant visit occurs.

The end of the study is defined as the date of the last visit of the last participant in the study.

5.4. Scientific Rationale for Study Design

This study is being conducted to fulfill regulatory requirements and is intended to further inform on the safety and effectiveness and PK of DTG/3TC FDC in adolescent participants and is intended to supplement the adequate and well-controlled data set being generated in adult participants, an open-label trial is appropriate. This study is not powered to test an efficacy hypothesis and is intended to generate safety and descriptive efficacy data; therefore a comparator is not relevant.

5.5. Dose Justification

The efficacy, PK, safety, and drug interaction potential of DTG and 3TC as individual agents have been evaluated in extensive clinical development programs. DTG and 3TC are approved and marketed as TIVICAY 50 mg once daily and EPIVIR 300 mg once daily, respectively. In addition, the fixed dose combination of DTG plus 3TC is approved in the United States, Canada and EU and is marketed as DOVATO.

The use of DTG plus 3TC (50 mg/300 mg) is supported by the approved 3TC 300 mg total daily dose for children weighing ≥25 kg , which may be taken as 150 mg BID or 300 mg once daily [EPIVIR™ Package Insert, 2020]; and DTG PK data from the paediatric ODYSSEY study. The ODYSSEY study is an open-label, randomized, non-inferiority, Phase II/III, trial comparing the efficacy and safety of DTG-based ART versus standard of care in children aged less than 18 years who are starting first-line ART or switching to second-line ART. A crossover PK substudy within ODYSSEY provided within-patient comparative PK and safety data in children weighing 25 kg to ≤40 kg,

switching from 25 mg and 35 mg DTG film coated tablet (FCT) doses to the adult 50 mg FCT dose, in order to simplify DTG administration. Data from this substudy indicate that in children weighing 25 kg to less than 40 kg, DTG 50 mg achieve appropriate plasma exposure as Ctrough and AUC0-24 h were comparable to DTG exposures in adults on 50 mg daily. For children weighing 25 kg to less than 30 kg, after switching from DTG 25 mg to DTG 50 mg, Ctrough and AUC0-24h values were 0.75(42) mg/L and 58.7(27) h*mg/L respectively. For children weighing 30 kg to less than 40 kg, after switching from DTG 35mg to DTG 50 mg, Ctrough and AUC0-24h values were 0.63(49) mg/L and 53.5(32) h*mg/L respectively. For adults, DTG 50 mg Ctrough and AUC0-24 h reference values (VIKING study, 112961) were 0.83(26) mg/L and 43.4(20) h*mg/L respectively. [Turkova, 2018].

6. STUDY POPULATION

The following are study specific eligibility criteria unless stated otherwise. In addition to these criteria, Investigators must exercise clinical discretion regarding selection of appropriate study participants for a trial of an oral medication, taking into consideration any local treatment practices or guidelines and good clinical practice (GCP).

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on DTG/3TC that may impact participant eligibility is provided in the DTG IB and the product labels for TIVICAY, EPIVIR and DOVATO. To assess any potential impact on participant eligibility with regard to safety, the investigator must refer to the IB and supplements, approved product labels, and/or local prescribing information for detailed information regarding warnings, precautions, contraindications, AEs, drug interactions, and other significant data pertaining to the study drugs.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or participant safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Participants are allowed to re-screen for this study one time, except where exclusionary HIV-1 resistance was present; re-screening will require a new participant screening number.

With the exception of a disqualifying viral genotype, a single repeat test (re-test) per analyte or assessment is allowed during the screening period to determine eligibility. Laboratory results provided from the central laboratory services will be used to assess eligibility.

The screening period for this study is defined as 28 days prior to the first dose of study medication. In cases of central laboratory assay failure or shipment failure, the screening period may be extended to 35 days to accommodate sample analysis and reporting. Approval of the Medical Monitor is required.

The study team will monitor gender distribution during the recruitment period to ensure adequate numbers of females and males are included in this study.

6.1. Inclusion Criteria

Eligible participants must:

be able to understand and comply with protocol requirements, instructions, and restrictions;

- be likely to complete the study as planned;
- be considered appropriate candidates for participation in an investigative clinical trial with oral medication (e.g. consideration of substance abuse, no acute major organ disease, no significant gastrointestinal disturbance that would interfere with absorption, etc.).

It is the responsibility of each investigator to carefully assess participants for suitability for participation in a clinical trial of an investigational agent. This includes assessment of physical and mental conditions, including substance abuse, which could significantly impact ability to complete protocol visits and assessments. Additionally, investigators must understand and be prepared to manage potential barriers to appropriate compliance with trial assessments.

A participant will be eligible for inclusion in this study only if all of the following criteria apply:

AGE AND WEIGHT
1. HIV-1 infected adolescents ≥12 to <18 years of age at the time of signing the informed consent form. 2. Weight ≥25 kg at the time of signing the informed consent form.
TYPE OF PARTICIPANT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
3. Screening plasma HIV-1 RNA between 1,000 and ≤500,000 c/mL. 4. Antiretroviral-naïve (defined as no prior therapy with any antiretroviral agent for the treatment of HIV following a diagnosis of HIV-1 infection). - Participants who received antiretroviral therapy for prevention of mother to child transmission of HIV in the first 3 months of life are allowed. - Participants who received HIV post-exposure prophylaxis (PEP) or pre-exposure prophylaxis (PrEP) in the past are allowed as long as the last PEP/PrEP dose was >6 months from HIV diagnosis or there is documented HIV seronegativity at least 2 months after the last prophylactic dose and prior to the date of HIV diagnosis. The study site must have documentation of the seronegative test available and placed into the study source documents.

SEX
5. Male or female. A female participant is eligible to participate if she is not pregnant (as confirmed by a negative serum human chorionic gonadotrophin (hCG) test at Screening and negative urine hCG test before Enrollment) and not lactating. Female participants who are of child bearing potential and who are engaging in sexual activity that could lead to pregnancy, must agree to use one of the birth control methods listed in Appendix 10 (Section 12.10) from 28 days prior to the first dose of study medication, and until 4 weeks after the last dose of study medication (and completion of the Follow-up visit). Condoms are recommended in addition, because their appropriate use is the only contraception method effective for preventing HIV-1 transmission. The investigator is responsible for ensuring that participants understand how to properly use these methods of contraception. All participants participating in the study should also 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
6. The participant's parent(s) or legal guardian or the participant is capable of giving signed informed consent as described in Section 12.4.3 which includes compliance with the requirements and restrictions listed in the consent form and in this protocol. Where applicable, participants must provide written assent.

6.2. Exclusion Criteria

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

CONCURRENT CONDITIONS/MEDICAL HISTORY
1. Females who are breastfeeding or plan to become pregnant or breastfeed during the study. 2. Any evidence of an active Centers for Disease Control and Prevention (CDC) Stage 3 and/or Category C or WHO Stage 4 disease (Appendix 6, Section 12.6), except cutaneous Kaposi's sarcoma not requiring systemic therapy and historical or current CD4 cell counts less than 200 cells/mm^3 or CD4% <15%. 3. Participants with severe hepatic impairment (Class C) as determined by Child-Pugh classification (Section 12.2). 4. Unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent

jaundice), cirrhosis, known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).

5. Evidence of HBV infection based on the results of testing at Screening for HBV surface antigen (HBsAg), HBV core antibody (anti-HBc), HBV surface antibody (anti-HBs or HBsAb), and HBV DNA as follows:

   - Participants positive for HBsAg are excluded;
   - Participants negative for anti-HBs but positive for anti-HBc (negative HBsAg status) and positive for HBV DNA are excluded.

     NOTE: Participants positive for anti-HBc (negative HBsAg status) and positive for anti-HBs (past and/or current evidence) are immune to HBV and are not excluded (See Section 12.11, Appendix 11: Decision Flow- Screening Tests for Hepatitis B Virus Serology, Interpretation and Action).

6. Anticipated need for any HCV therapy during the first 48 weeks of the study and for HCV therapy based on interferon or any drugs that have a potential for adverse drug:drug interactions with study treatment throughout the entire study period.

7. Untreated syphilis infection (positive rapid plasma reagin [RPR] at Screening without clear documentation of treatment). Participants who are at least 24 hours post completed treatment are eligible.

8. History or sensitivity to any of the study medications or their components or drugs of their class, or a history of drug or other allergy that in the opinion of the Investigator or Medical Monitor contraindicates participation.

9. Ongoing malignancy other than cutaneous Kaposi's sarcoma, basal cell carcinoma, or resected, non-invasive cutaneous squamous cell carcinoma, or cervical, anal or penile intraepithelial neoplasia; other localized malignancies require agreement between the investigator and the Study Medical Monitor for inclusion of the participant.

10. Participants who in the investigator’s judgment, poses a significant suicidality risk. Recent history of suicidal behavior and/or suicidal ideation may be considered as evidence of serious suicide risk.

EXCLUSIONARY TREATMENTS PRIOR TO SCREENING OR DAY 1
11. Treatment with an HIV-1 immunotherapeutic vaccine within 90 days of Screening.
12. Treatment with any of the following agents within 28 days of Screening i. radiation therapy, ii. cytotoxic chemotherapeutic agents,

iii. any systemic immune suppressant;

13. Treatment with any agent with documented activity against HIV-1 *in vitro* within 28 days of first dose of study treatment.

14. Receipt of any prohibited mediation listed in Section 7.9.2 and inability or unwillingness to switch to an alternative medication.

15. Exposure to an experimental drug or experimental vaccine within either 28 days, 5 half-lives of the test agent, or twice the duration of the biological effect of the test agent, whichever is longer, prior to the first dose of study treatment.

LABORATORY VALUES OR CLINICAL ASSESSMENTS AT SCREENING

16. Any evidence of pre-existing viral resistance based on the presence of any major resistance-associated mutation [International Antiviral Society -USA, 2017] in the Screening result or, if known, in any historical resistance test result. NOTE: retests of disqualifying Screening genotypes are not allowed.

17. Any verified Grade 4 laboratory abnormality. A single repeat test is allowed during the Screening period to verify a result.

18. Any acute laboratory abnormality at Screening, which, in the opinion of the Investigator, would preclude the participant's participation in the study of an investigational compound.

19. Alanine aminotransferase (ALT) ≥5 times the upper limit of normal (ULN) or ALT ≥3xULN and bilirubin ≥1.5xULN (with >35% direct bilirubin).

20. Creatinine clearance of <50 mL/min/1.73 m^2 using the Schwartz equation method.

OTHER CRITERIA

21. Children who are wards of the state or government.

6.3. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs) (see Section 9.3.1).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened for this study one time within 30 days, except where exclusionary HIV-1 resistance was present; re-screening will require new screening number.

Retesting of an exclusionary laboratory result, except for exclusionary HIV-1 resistance, is allowed during the screening period and does not require a new screening number.

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. In this trial, study treatment will be the fixed dose combination of DTG/3TC.

7.1. Treatments Administered

	Study Treatment
Product name:	**DTG + 3TC FDC**
Formulation description:	Clinical Trial Material
Dosage form:	Tablet
Unit dose strength(s)/Dosage level(s):	50 mg/300 mg
Route of Administration:	Oral
Dosing instructions:	Take one tablet daily.

7.2. Dose Modification

Not applicable.

7.3. Treatment Assignment

Participants will be centrally enrolled using an Interactive Voice/Web Response System (IVRS/IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log in information and directions for the IWRS will be provided to each site.

Study treatment will be dispensed at the specified study visits summarized in the SoA. Returned study treatment will not be re-dispensed to participants.

Informed consent must be obtained prior to any study procedures, including any screening assessment. Eligible participants will be provided open-label study treatment. Study enrollment will be facilitated by the interactive voice/web recognition system (IVRS/IWRS). Following confirmation of fulfilment of study entry criteria, study site

personnel will be required to contact the IVRS/IWRS to enroll participants. Each participant will be assigned a unique identifier and a unique treatment number. Participants will maintain the same study treatment through study discontinuation. Participants who are enrolled into the study and subsequently withdrawn may not be rescreened. Once a participant number has been assigned it must not be re-assigned.

7.4. Blinding

This is an open-label, single-arm study, therefore blinding will not be used.

7.5. Packing and Labeling

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

7.6. Preparation/Handling/Storage/Accountability

- 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. All study treatment 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 (ie, receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study treatment are provided in the Investigator site file.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from ViiV Healthcare/GSK.

7.7. Compliance with Study Treatment Administration

Compliance with study treatment will be assessed through querying the participant during the site visits and documented in the source documents and eCRF. Study treatment accountability will be evaluated using pill counts of unused study treatment (DTG/3TC). This assessment will be conducted each time the participant receives a new (refill) supply of study treatments through the Withdrawal visit or study completion. These data will be recorded in the participant's eCRF and may be summarized for analysis purposes.

Additionally, at each visit, participants will be asked about missed doses and the primary reasons or barriers for missing doses. Answers to these queries will be recorded in the eCRF and summarized.

7.8. Study Treatment Overdose

For this study, any tablet intake exceeding the prescribed daily number of tablets for study treatment, e.g. more than one tablet, will be considered an overdose (see [TIVICAY Package Insert, 2020]; [EPIVIR Package Insert, 2020]). The Investigator should use clinical judgment in treating overdose, as ViiV Healthcare/GSK is unable to recommend specific treatment.

For the purposes of this study, an overdose is not an AE (see Section 9.3.1) unless it is accompanied by a clinical manifestation associated with the overdose. If the clinical manifestation presents with serious criteria, the event is an SAE (see Section 9.3.1).

If an overdose occurs and is associated with an adverse event requiring action, study medications should be temporarily discontinued until the adverse event resolves.

7.9. Concomitant Therapy

Participants should be advised to notify their investigator of any current or proposed concomitant medication, whether prescribed or over-the-counter, because of the potential drug:drug interactions between such treatments and the study drugs. The investigator should evaluate any potential drug:drug interactions at every visit, including reviewing the most current version of the U.S. and local prescribing information for DTG and 3TC, especially if any new concomitant medications are reported by participants. All concomitant medications taken during the study will be recorded in the eCRF.

If any treatments for Coronavirus Disease-2019 (COVID-19) are planned for a study participant, please consult with the Study Medical Monitor to ensure that relevant drug interactions are considered and to ensure that continued study participation remains appropriate. Refer to Section 12.12 (Appendix 12 COVID-19 Guidance) for safety reporting requirements and instruction for data capture.

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

7.9.1. Permitted Medications and Non-Drug Therapies

Concomitant medications (prescription and non-prescription) should be administered only as medically necessary during the study (except prohibited medications described in Section 7.9.2). Chemoprophylaxis for HIV-associated conditions is encouraged, if appropriate, at the discretion of the participant and their physician. All concomitant medications, blood products, and vaccines taken during the study will be recorded in the eCRF with dates of administration.

Because non-HIV vaccines may cause a temporary increase in the level of HIV-1 plasma RNA, it is highly recommended that a vaccine, if necessary, be given during or

immediately after a scheduled visit after all samples for laboratory tests have been drawn and only when scheduled visits are ≥4 weeks apart. This approach will minimize the risk of non-specific increases in the level of HIV-1 plasma RNA at the next scheduled assessment.

DTG/3TC should be administered 2 hours before OR 6 hours after taking antacid or laxative products or sucralfate containing polyvalent cations (e.g. aluminium and magnesium) or calcium supplements. Proton pump inhibitors and H2-antagonists may be used in place of antacids with no scheduling restrictions. Concurrent administration with multivitamins is acceptable. Iron supplements can be taken with study treatment provided that all are taken together with a meal. Under fasted conditions, DTG/3TC should be given 2 hours prior to OR 6 hours after calcium or iron supplements.

Metformin concentrations may be increased by DTG. A dose adjustment of metformin should be considered when starting and stopping co-administration of DTG/3TC with metformin, to maintain glycemic control.

Clinical monitoring is recommended for participants taking methadone as methadone maintenance therapy may need to be adjusted in some participants.

Non-protocol defined treatments or medical interventions (e.g., physical therapy, radiotherapy, surgical procedures) are permitted during the study for appropriate medical management of the participant.

7.9.2. Prohibited Medications and Non-Drug Therapies

The following concomitant medications or therapies are not permitted at any time during the study:

- HIV immunotherapeutic vaccines are not permitted at any time during the study (see Section 7.9.1 for guidance regarding non-HIV vaccines).
- Other experimental agents, ART drugs not otherwise specified in the protocol, cytotoxic chemotherapy, or radiation therapy (see Exclusion Criteria, Section 6.2).
- Systemically administered immunomodulators (such as interleukin and interferon agents) are prohibited (a list of examples is provided in the Investigator site file). This includes topical agents with substantial systemic exposure and systemic effects. Use of topical imiquimod is permitted.
- HCV therapy during the study is prohibited during the first 48 weeks; interferon-based HCV therapy and HCV therapy based any drugs that have a potential for adverse drug:drug interactions with study treatment are prohibited throughout the entire study.
- Chronic use of systemic (oral or parenteral) glucocorticoids must be avoided; however, topical, inhaled or intranasal use of glucocorticosteroids of any duration will be allowed. Short treatment courses (14 days or less) of oral prednisone/ prednisolone/methylprednisolone are allowed.

- For participants with an **unanticipated** requirement for HCV therapy during study, interferon or any other medications that have a potential for adverse drug-drug interactions with study treatment are prohibited during the conduct of the study.
- Acetaminophen is not to be used in patients with acute viral hepatitis [James, 2009].
- The following medications or their equivalents may cause decreased concentrations of DTG and therefore must not be administered concurrently with DTG/3TC.
- Carbamazepine
- Oxcarbamazepine
- Phenobarbital
- Phenytoin
- Rifampicin or rifapentine
- St. John's wort (*Hypericum perforatum*)

Dofetilide, pilsicainide and fampridine (also known as dalfampridine) are prohibited as DTG may inhibit their renal tubular secretion resulting in increased dofetilide/pilsicainide/fampridine concentrations and potential for toxicity.

NOTE: Any prohibited medications that substantially decrease DTG concentrations should be discontinued for a minimum of four weeks or a minimum of three half-lives (whichever is longer) prior to the first dose and any other prohibited medications should be discontinued for a minimum of two weeks or a minimum of three half-lives (whichever is longer) prior to the first dose.

For information on concurrent therapies and interactions suspected to be relevant to other antiretroviral therapy in the regimen, please consult the local prescribing information.

7.10. Treatment after the End of the Study

The investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition, whether or not ViiV Healthcare is providing specific post-study treatment.

Participants who successfully complete 48 weeks of treatment will have the opportunity to continue to receive DTG/3TC through Week 144 in the study Extension Phase.

If required by local regulations, study participants who have successfully completed both the Treatment Phase through 48 weeks and the Extension Phase through Week 144 will be given the opportunity to continue to receive DTG/3TC once daily in the Continuation Phase until:

- DTG and 3TC are both locally approved for use as part of a dual regimen, and the single entities of DTG and 3TC are available to patients (e.g. through public health services), or
- the DTG/3TC FDC tablet, if required by local regulations, is locally approved and available (e.g. commercially or through public health services), or

- the participant no longer derives clinical benefit, or
- the participant meets a protocol-defined reason for discontinuation, or
- development of the DTG plus 3TC dual regimen is terminated.

Participants completing the Continuation Phase must return to the clinic for a final End of Continuation Phase Visit when transitioning to locally approved available supply. At this final visit, the site will conduct study assessments noted within the End of Continuation Phase Visit column of the SOA (See Section 2).

8. DISCONTINUATION CRITERIA

Participants permanently discontinuing study treatment are considered to be withdrawn from the study. Similarly, participants who enter the Extension Phase and Continuation Phase but permanently discontinue participation prior to transitioning to commercially available DTG + 3TC are considered to be withdrawn from study treatment and from the study. Withdrawn participants will not be replaced.

8.1. Discontinuation of Study Treatment

8.1.1. Virologic Criteria for Withdrawal, Participant Management and Viral Resistance Testing

For the purposes of clinical management in this study, **suspected virologic withdrawal (SVW)** and **confirmed virologic withdrawal (CVW)** criteria are defined here wherein the virologic withdrawal criteria revolve around the HIV-1 RNA cut-off of 200 c/mL.

8.1.1.1. Virologic Withdrawal Criteria

Suspected Virologic Withdrawal criteria

- A single HIV-1 RNA value as defined by Virologic Non-response or Virologic Rebound (see below)

Confirmed Virologic Withdrawal criteria

- A second and consecutive HIV-1 RNA value meeting Virologic Non-response or Rebound

Virologic withdrawal criteria must be confirmed for each criterion by a repeat and consecutive plasma HIV-1 RNA measurement between 2 and 4 weeks after the participant met a SVW criterion unless a delay is necessary to meet the requirements of confirmatory HIV-1 RNA testing as described below in Section 8.1.1.2. For the purposes of clinical management in this study, virologic withdrawal criteria are defined as any of the following:

Virologic Non-response

- A decrease in plasma HIV-1 RNA of less than 1 log10 c/mL at or after Week 12, with subsequent confirmation, unless plasma HIV-1 RNA is <200 c/mL.

- Confirmed plasma HIV-1 RNA levels ≥200 c/mL at or after Week 24.

Virologic Rebound

- Confirmed rebound in plasma HIV-1 RNA levels to ≥200 c/mL after prior confirmed suppression to <200 c/mL.

Participants who meet any CVW criterion must be discontinued from the study.

Cases of participants meeting CVW criteria will trigger virologic resistance testing. Investigators should use their discretion as to the most appropriate clinical management of their participants if more stringent local guidelines apply.

8.1.1.2. Managing Participants Meeting Suspected Virologic Withdrawal Criteria

Only plasma HIV-1 RNA values determined by the central laboratory will be used to assess virologic withdrawal criteria. Upon notification that a participant's HIV-1 RNA plasma level qualifies him/her as meeting an SVW criterion, the Investigator should query the participant regarding intercurrent illness, recent immunisation, or interruption of therapy as inadequate adherence is a common cause of elevated HIV-1 RNA measurements.

All cases that meet an SVW criterion must be confirmed by a second measurement performed <u>at least 2 weeks but not more than 4 weeks apart</u> from the date of the original sample, <u>unless</u> a delay is necessary to meet the requirements of confirmatory HIV-1 RNA testing as outlined below.

The following guidelines should be followed for scheduling confirmatory HIV-1 RNA testing in an effort to avoid false-positive results:

- Confirmatory testing should be scheduled 2 to 4 weeks following resolution of any intercurrent illness, during which time the participant should receive full doses of all study drugs.
- Confirmatory testing should be scheduled at least 4 weeks following any immunisation, during which time the participant should receive full doses of study drugs.
- If therapy is interrupted due to **<u>toxicity management, non-compliance, or other reasons, confirmatory testing should be scheduled 2 to 4 weeks following resumption of full doses of study drugs.</u>**
- The participant should have received full doses of study drugs for at least 2 weeks at the time confirmatory plasma HIV-1 RNA is done.

Sites should contact Medical Monitor to discuss individual participants, whenever necessary.

8.1.1.3. Managing Participants Meeting Confirmed Virologic Withdrawal Criteria

Once a participant has been confirmed as meeting a virologic withdrawal criterion, the 'plasma for storage' sample from the time of meeting SVW criteria and the Day 1 sample

will be sent as soon as possible for genotypic and phenotypic resistance testing and the result made known to the Investigator if and when available.

Note: shipment of storage samples must occur promptly following confirmation of a virologic withdrawal criterion and separately from other samples drawn in real time at any visit.

Participants may continue to receive study drug at the discretion of the investigator until results of resistance testing are available at which time the participant must be withdrawn from the study, except in cases where participant samples have HIV-1 RNA <500 c/mL as noted below. **A participant who meets a CVW criterion must be discontinued from the study.**

The protease (PR)/reverse transcriptase (RT)/integrase assays used in this study are not validated for plasma HIV-1 RNA levels <500 c/mL. Nevertheless, for all participants who meet CVW Criteria, additional plasma samples will be analysed in an attempt to obtain genotype/phenotype data on as many samples as possible. Participants with confirmed HIV-1 RNA levels between 200 c/mL and <500 c/mL should be transitioned off study drug within 30 days even if no resistance testing data becomes available, as genotype/phenotype data may not be reliably generated from plasma samples collected from these participants.

If a participant is prematurely discontinued from participation in the study, the Investigator must make every effort to perform the evaluations outlined in the Time and Events Schedule (Section 2). These data will be recorded, as they comprise an essential evaluation that needs to be done before discharging any participant from the study.

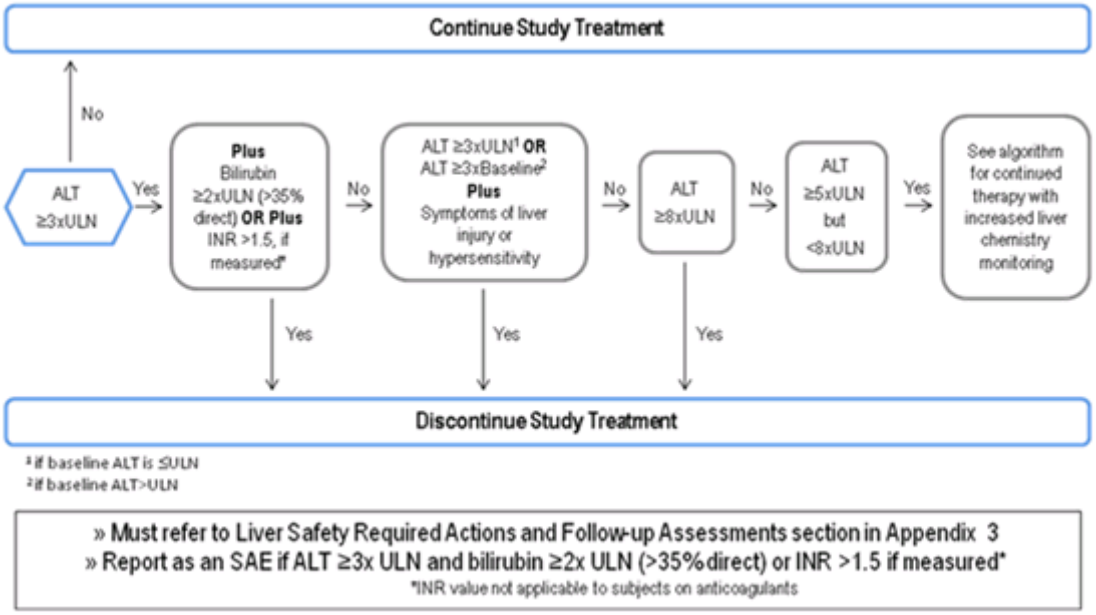
8.1.2. Liver Chemistry Stopping Criteria

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).

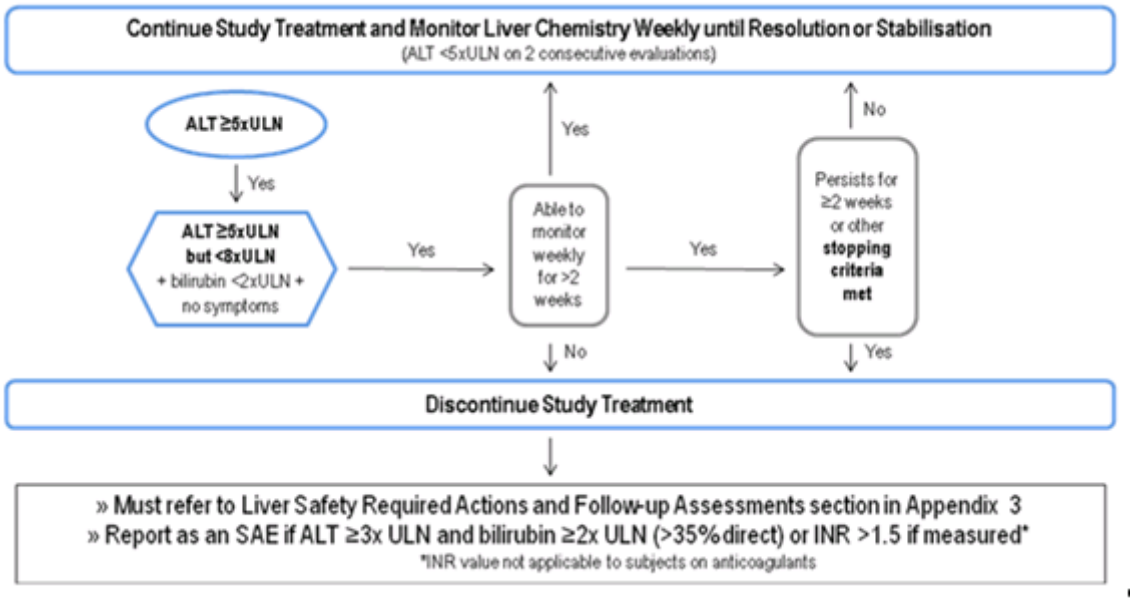
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Discontinuation of study treatment for abnormal liver tests should be considered by the investigator when a participant meets one of the conditions outlined below or if the investigator believes that it is in the best interest of the participant.

Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT ≥5xULN but <8xULN



Liver Safety Required Actions and Follow up Assessments Section can be found in Section 12.3.

8.1.3. Temporary Discontinuation of Study Treatment

Participants may have a temporary interruption to their study treatment for management of toxicities. Such interruption of study treatment does not require withdrawal from the study. However, consultation with the Medical Monitor is required.

8.1.4. Study Treatment Restart or Rechallenge

If a participant meets liver chemistry stopping criteria do not restart/rechallenge the participant with study treatment unless:

- ViiV Healthcare Safety and Labelling Committee (VSLC) approval **is granted**,
- Ethics and/or Institutional Review Board (IRB) approval is obtained, if required, and
- Separate consent for treatment restart/rechallenge is signed by the participant.

Refer to Appendix 5, Section 12.5 for full guidance.

8.2. Withdrawal from the Study and Stopping Criteria

A participant may withdraw from study treatment at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If a participant withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records. Withdrawn participants will not be replaced.

Participants are not obligated to state the reason for withdrawal. However, the reasons for withdrawal, or failure to provide a reason, must be documented by the Investigator on the Completion/Withdrawal section of the electronic case report form (eCRF). Every effort should be made by the Investigator to follow up participants who withdraw from the study.

Participants may have a temporary interruption to their study treatment for management of toxicities. Such interruption of study treatment does not require withdrawal from the study. However, consultation with the Medical Monitor is required.

Participants <u>may</u> be prematurely discontinued from the study for any of the following reasons:

- Participant or Investigator non-compliance ;
- At the request of the participant, Investigator, GSK or ViiV Healthcare;
- The participant requires concurrent prohibited medications during the course of the study. The participant may remain in the study if in the opinion of the Investigator and the Medical Monitor such medication will not interfere with the conduct or interpretation of the study or compromise the safety of the participant.
- The participant becomes a ward of State or any other agency, institution or entity. The site Investigator must notify the Study Medical Monitor immediately if a participant's guardianship status changes such that they become a ward during the study. If this occurs, the ViiV Chief Medical Officer must determine if the participant may continue in the study.

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

- Virologic failure criteria as specified in Section 8.1.1.1 are met;
- Participant requires substitution or dose modification of DTG or 3TC;
- Liver toxicity where stopping criteria specified in Section 8.1.2 are met and no compelling alternate cause is identified;
- Renal toxicity criteria as specified in Appendix 9 (Section 12.9.1.3) are met and no compelling alternate cause is identified;
- Grade 4 clinical AE considered causally related to study drug (Appendix 9, Section 12.9);
- Allergic reaction or rash criteria as specified in Appendix 9 (Section 12.9.1.5) are met and no compelling alternate cause is identified;
- Pregnancy (intrauterine), regardless of termination status of pregnancy (Section 9.3.2). As a reminder, females of reproductive potential who changed their minds and desire to be pregnant, or who state they no longer are willing to comply with the approved pregnancy avoidance methods, should also be withdrawn from the study.
- If a participant is prematurely or permanently withdrawn from the study, the procedures described in the SoA (Section 2) for the Withdrawal visit – and if necessary, the Follow Up visit – are to be performed.

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 considered 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.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will be described in the study informed consent form.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1. Screening and Critical Baseline Assessments

Written and informed consent must be obtained from each potentially eligible participant's legal guardian (or by the participant as required by local law) by study site personnel prior to the initiation of any Screening procedures as outlined in this protocol. Where appropriate, participants must also provide written assent. Note: where "informed consent" is referred to in this protocol, the term covers both written consent and assent, where applicable. The consent form and assent form must have been approved by the IRB/Independent Ethics Committee (IEC). After providing written informed consent, participants will complete Screening assessments to determine participant eligibility. Each participant being screened for study enrolment evaluation will be assigned a participant screening number at the Screening visit. This number will be given sequentially in chronological order of participant presentation.

9.1.1. Screening Assessments

Assessment to be conducted as Screening assessments are provided in the SOA Table (Section 2).

Eligibility criteria must be carefully assessed at the Screening visit. Physical examinations should be conducted as part of normal routine clinical care but will not be

collected systematically in the eCRF. Vital signs, height, weight and other baseline status information will be collected.

Medical and medication history will be assessed as related to the inclusion/exclusion criteria listed in Section 6.

Other information to be collected at Screening includes current medical conditions.

The following demographic parameters will be captured: year of birth, sex, race and ethnicity.

All participants must provide a plasma sample for determination of viral genotypic resistance by the central laboratory. For eligibility, the resistance report must show no evidence of primary viral resistance based on the presence of any major resistance-associated mutation [International Antiviral Society -USA, 2017]. The study virologists will confirm the lack or presence of exclusionary resistance mutations, and communicate eligibility based on the resistance test results.

Note: in cases of assay failure at the central laboratory, viral genotypic and phenotypic results from a locally available assay may be considered for eligibility. Prior discussion approval with the Medical Monitor will be required.

Severe hepatic impairment is exclusionary and will be assessed by Child-Pugh grading at Screening (see Appendix 2, Section 12.2).

CrCl is calculated at Screening, and participants with a CrCL <50 mL/min per 1.73 m^2 are excluded due to requirements for dose reduction of 3TC.

Participants with chronic active hepatitis B are excluded. Evidence of HBV infection is based on the results of testing at Screening for HBsAg, anti-HBc, anti-HBs (HBsAb), and HBV DNA. HBV DNA testing will only be performed during screening and prior to enrollment for participants with positive anti-HBc and both negative HBsAg and anti-HBs (past and/or current evidence).

All participants will be screened for syphilis using a rapid plasma reagin (RPR) at Screening. Participants with untreated syphilis infection, defined as a positive RPR without clear documentation of treatment, are excluded. Participants with a positive RPR test who have not been treated may be rescreened at least 24 hours after completion of antibiotic treatment for syphilis.

Participants who meet all entry criteria may be enrolled as soon as all Screening assessments are complete, and the results are available and documented. All participants will complete the Screening period of approximately 28 days prior to Baseline (Day 1) during which all clinical and laboratory assessments of eligibility must be performed and reviewed. All Screening results **must** be available prior to enrollment.

Participants not meeting all inclusion and exclusion criteria at initial screen may be rescreened and receive a new participant number one time unless they were excluded for reason of having exclusionary historic genotypic resistance. Participants who are

enrolled into the trial and subsequently withdrawn from the study for any reason may not be rescreened.

9.1.2. Baseline Assessments

Assessments to be conducted at Baseline (Day 1) are provided in the SOA Table (Section 2).

At Day 1 and prior to enrollment, any changes to the eligibility parameters must be assessed and any results required prior to enrollment (e.g. Day 1 urine pregnancy test for females) must be available and reviewed.

The electronic Columbia Suicidality Severity Rating Scale (eC-SSRS) must also be administered prior to enrollment.

Participants Co-infected with Hepatitis C Virus (HCV)

Investigators should consult current treatment guidelines when considering choice of therapy for participants with chronic HCV infection. Participants with an anticipated need for HCV therapy prior to the primary endpoint may not be enrolled into this study.

For participants with an **unanticipated** requirement for HCV therapy during the conduct of the study, the Investigator must consult with the medical monitor. HCV treatment based on interferon or any other medications that have a potential for adverse drug-drug interactions with study treatment, is prohibited during the conduct of the study (see Section 7.9.2).

9.2. Efficacy Assessments

Plasma HIV-1 RNA

Plasma for quantitative HIV-1 RNA will be collected according to the SoA Table (Section 2). Methods to be used may include but are not limited to the Abbott RealTime HIV-1 Assay with a lower limit of quantitation of 40 c/mL. In some cases (e.g. where the plasma HIV-1 RNA is below the lower limit of detection for a given assay) additional exploratory methods may be used to further characterize plasma HIV-1 RNA levels.

Lymphocyte Subsets

Lymphocyte subsets will be collected for assessment by flow cytometry (total lymphocyte counts, percentage, and absolute CD4+ cell counts) according to the SOA Table (Section 2).

HIV-1 Classification and HIV Associated Conditions

HIV-associated conditions will be recorded as per the SOA Table (Section 2). HIV associated conditions will be assessed according to the 2014 CDC Classification System for HIV Infection in Adults or, where most appropriate, the WHO Clinical Staging System of HIV/AIDS for Adults and Adolescents (see Appendix 6, Section 12.6). Indicators of clinical disease progression are defined as:

CDC Class A/WHO Stage 1 at enrolment → Stage 3 event;

CDC Class B/WHO Stage 2 at enrolment → Stage 3 event;

CDC Class C/WHO Stage 3 at enrolment → New Stage 3 Event;

CDC Class A, B, C/WHO Stage 1, 2 or 3 at enrolment → Death.

9.3. Safety Assessments

9.3.1. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 8 (Section 12.8).

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 treatment (see Section 12.8.6).

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

- All SAEs will be collected from the start of treatment until the follow-up visit or contact at the time points specified in the SoA (Section 2). Any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a ViiV Healthcare product will be recorded from the time a participant consents to participate in the study.
- All AEs will be collected from the start of treatment until the follow-up visit or 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 case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 8 (Section 12.8.6). 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 Medical Monitor.

- 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 (Section 12.8.6).

9.3.1.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

9.3.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 8 (Section 12.8).

9.3.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 8 (Section 12.8.3) and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the eCRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV eCRFs are presented as queries in response to reporting of certain CV Medical Dictionary for Regulatory Activities (MedDRA) terms. The CV information should be recorded in the specific cardiovascular section of the eCRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

9.3.1.5. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

The events or outcomes listed in the CDC Classification System for HIV-1 Infections (Appendix 6, Section 12.6) will be recorded on the HIV-Associated Conditions eCRF page if they occur. However, these individual events or outcomes, as well as any sign, symptom, diagnosis, illness, and/or clinical laboratory abnormality that can be linked to any of these events or outcomes are not reported to ViiV Healthcare/GSK/Pharmaceutical Product Development (PPD) as AEs and SAEs even though such event or outcome may meet the definition of an AE or SAE, **unless the following conditions apply**:

- The investigator determines that the event or outcome qualifies as an SAE under part 'f' of the SAE definition (see Section 12.8.2), or
- The event or outcome is in the investigator's opinion of greater intensity, frequency or duration than expected for the individual participant, or

- Death occurring for any reason during a study, including death due to a disease-related event, will always be reported promptly.
- Lymphomas and invasive cervical carcinomas are excluded from this exemption; they must be reported as SAEs even if they are considered to be HIV-related.

9.3.1.6. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to ViiV Healthcare or designee of a 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.
- ViiV Healthcare/GSK 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. ViiV Healthcare/GSK will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and ViiV Healthcare/GSK policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information eg, summary or listing of SAE) from ViiV Healthcare/GSK will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.3.2. Pregnancy

Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected in addition to the regular pregnancy testing required by the protocol.

Details of all pregnancies (intrauterine) in female participants will be collected after the start of study treatment and until the final Follow-up visit. Pregnancies that occur following the first dose of study drug will be reported to the Medical Monitor. Follow-up information will be collected for pregnancies occurring from Day 1 to the final Follow-up visit.

If a pregnancy is reported, the investigator should inform ViiV Healthcare/GSK/PPD within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 12.10.2.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. The pregnancy must be followed up to determine outcome

(including premature termination) and status of mother and child(ren). Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the participant has completed the study and considered by the investigator as possibly related to the study treatment must be reported promptly to ViiV Healthcare/GSK (or designee). GSK's central safety department will forward this information to the ART Pregnancy Registry. The international registry is jointly sponsored by manufacturers or licensees of ARV products. Additional information and a list of participating manufacturers/licensees are available from http://www.apregistry.com/.

9.3.3. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

The events or outcomes listed in the CDC Classification System for HIV-1 Infections (Appendix 6, Section 12.6) will be recorded on the HIV-Associated Conditions eCRF page if they occur. However, these individual events or outcomes, as well as any sign, symptom, diagnosis, illness, and/or clinical laboratory abnormality that can be linked to any of these events or outcomes are not reported to ViiV Healthcare/GSK as AEs and SAEs even though such event or outcome may meet the definition of an AE or SAE, **unless the following conditions apply**:

- The investigator determines that the event or outcome qualifies as an SAE under part 'f' of the SAE definition (Section 12.8.2) or
- The event or outcome is in the investigator's opinion of greater intensity, frequency or duration than expected for the individual participant, or
- Death occurring for any reason during a study, including death due to a disease-related event, will always be reported promptly.

Lymphomas and invasive cervical carcinomas are excluded from this exemption; they must be reported as SAEs even if they are considered to be HIV-related.

If either of the above conditions is met then record the Disease Related Event on the SAE page rather than the HIV Associated Conditions eCRF page and report promptly to PPD/ViiV Healthcare/GSK.

9.3.4. Suicidal Risk Monitoring

Participants with HIV infection occasionally may present with symptoms of depression and/or suicidality (suicidal ideation or behavior). In addition, there have been some reports of depression, suicidal ideation and behavior (particularly in patients with a pre-existing history of depression or psychiatric illness) in some patients being treated with INIs, including DTG. Therefore, it is appropriate and important to monitor participants for suicidality before and during treatment.

Participants should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. It is recommended that the investigator consider mental health consultation or referral for participants who experience signs of suicidal ideation or behavior. Participants presenting with new onset/treatment emergent depression should be advised to contact the investigator immediately if symptoms of severe acute depression (including suicidal ideation/attempts) develop, because medical intervention and discontinuation of the study medication may be required. Consideration should be given to discontinuing DTG/3TC in participants who experience signs of suicidal ideation or behavior.

Assessment of treatment-emergent suicidality will be monitored during this study using the electronic version of the Columbia Suicidality Severity Rating Scale (eC-SSRS). The definitions of behavioral suicidal events used in this scale are based on those used in the Columbia Suicide History Form [Posner, 2007]. Questions are asked on suicidal behavior, suicidal ideation, and intensity of ideation. Day 1 (Baseline) visit questions will be in relation to lifetime experiences and current experiences (within the past 2 months); all subsequent questioning is in relation to the last assessment. The eC-SSRS is to be administered as a patient completed questionnaire specified in the SOA Table (Section 2). The eC-SSRS will be conducted electronically by telephone or by computer/tablet connected to the internet.

Additionally, the investigator will collect information using the Possible Suicidality-Related AE (PSRAE) eCRF form in addition to the AE (non-serious or SAE) eCRF form on any participant that experiences a possible suicidality-related AE while participating in this study. This may include, but is not limited to, an event that involves suicidal ideation, a preparatory act toward imminent suicidal behavior, a suicide attempt, or a completed suicide. The investigator will exercise his or her medical and scientific judgment in deciding whether an event is possibly suicide-related. PSRAE forms should be completed and reported to ViiV Healthcare/GSK within 1 week of the investigator diagnosing a possible suicidality-related AE.

Families and caregivers of participants being treated with DTG/3TC should be alerted about the need to monitor participants for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior and to report such symptoms immediately to the study investigator.

9.4. Treatment of Overdose

For this study, any tablet intake exceeding the protocol-define daily dose (i.e. 1 tablet) will be considered an overdose (see [TIVICAY Product Information, 2020]; [EPIVIR Product Information, 2020]). The Investigator should use clinical judgment in treating overdose, as ViiV Healthcare/GSK is unable to recommend specific treatment.

For the purposes of this study, an overdose is not an AE (see Section 12.8.1) unless it is accompanied by a clinical manifestation associated with the overdose. If the clinical manifestation presents with serious criteria, the event is an SAE (see Section 12.8.2).

If the overdose was intentional, please refer to Section 9.3.4 (Suicidal Risk Monitoring) which provides instruction for the collection of possible suicidality related AE information.

If an overdose occurs and is associated with an adverse event requiring action, all study medications should be temporarily discontinued until the adverse event resolves.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until DTG/3TC can no longer be detected systemically (at least 2 days).
3. Obtain a plasma sample for PK analysis within 60 hours 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.

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

9.4.1. Physical Examinations

Physical exams should be conducted as part of normal routine clinical care but will not be collected systematically in the eCRF. Abnormalities noted during any exam must be recorded in the eCRF (e.g. in the current medical conditions or AE logs).

9.4.2. Electrocardiograms

A 12-lead ECG will be performed at Screening for possible use as a reference during the study (i.e. in evaluation of any pertinent cardiovascular event).

9.4.3. Clinical Safety Laboratory Assessments

- The list of clinical laboratory tests to be performed is below; refer 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 5 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 below must be conducted in accordance with the laboratory manual and the SoA.

Table 1 Protocol Required Safety Laboratory Assessments

Hematology:			
Platelet count		Automated WBC differential:	
RBC count		Neutrophils	
WBC count (absolute)		Lymphocytes	
Hemoglobin		Monocytes	
Hematocrit		Eosinophils	
MCV		Basophils	
MCH			
Clinical Chemistry:			
BUN	Potassium	AST	Total bilirubin[a]
Creatinine	Chloride	ALT	Albumin
Glucose[b]	Total CO2	Alkaline phosphatase	Creatine phosphokinase
Sodium		Phosphate	GFR/Creatinine clearance[c]
Calcium		Protein	Cystatin-C (Day 1 only)
Fasting Lipid Panel[d]			
Total cholesterol			
HDL cholesterol			
LDL cholesterol			
Triglycerides			
Urinalysis			
specific gravity, pH, glucose, protein, blood and ketones by dipstick (with microscopic examination if blood or protein is abnormal), urine albumin/creatinine ratio, urine protein/creatinine ratio, urine phosphate			
Other Tests			
Plasma HIV-1 RNA[e]			
CD4+ and CD8+ lymphocyte counts (including CD4:CD8 ratio)			
Hepatitis B (HBsAg, anti-HBc, anti-HBs, HBV DNA)			
Hepatitis C (anti-HCV)			
PT/INR			
RPR			
HbA1c			
Pregnancy test for females of childbearing potential[f]			

MCV = mean corpuscular volume, RBC = red blood cells, WBC = white blood cells, BUN = Blood urea nitrogen, AST=aspartate aminotransferase, ALT = alanine aminotransferase, CO_2 = carbon dioxide, HbA1c = glycated haemoglobin, HDL = high density lipoprotein, LDL = low density lipoprotein, HbsAg= hepatitis B virus surface antigen, PT/INR = prothrombin time/international normalized ratio, RPR = Rapid Plasma Reagin.

a. Direct bilirubin will be reflexively performed for all total bilirubin values >1.5 × ULN.
b. For fasting glucose assessments, an overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable for participants with afternoon appointments.

c. Glomerular filtration rate (GFR) will be estimated by the central laboratory using the Bedside Schwartz equation [Schwartz, 2009]. In addition, GFR will be estimated by the central laboratory using Creatinine-Cystatin C-Based CKiD Equation [Schwartz, 2012] at day 1 and when indicated by renal toxicity criteria.
d. For fasting lipids assessments, an overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable for participants with afternoon appointments.
e. For participants meeting virologic withdrawal criteria, plasma samples will be analyzed in attempt to obtain genotype/phenotype data.
f. Urine pregnancy test/ serum pregnancy test will be performed according to the SoA (Section 2).

9.5. Viral Genotyping and Phenotyping

Whole venous blood samples will be obtained from each participant to provide plasma for storage samples according to the SoA in Section 2 (for potential viral genotypic and phenotypic analyses). Participants meeting confirmed virologic failure criteria will have plasma samples tested for HIV-1 PR and RT genotype and phenotype and HIV-1 integrase (IN) genotype and phenotype from Baseline samples and from samples collected at the time of meeting suspected virologic failure criteria; these results will be reported to the investigator as soon as available to provide guidance for election of an alternative regimen.

Details concerning the handling, labelling and shipping of these samples will be supplied separately. Genotypic analyses for RT and PR will be carried out at Screening by Q^2 Solutions, or Monogram Biosciences if needed due to technical issues, and on-study genotypic and phenotypic analyses may be carried out by Monogram Biosciences using, but not limited to, their Standard PhenoSense and GenoSure testing methods for RT and PR.

9.5.1. HIV-1 Polymerase Viral Genotyping and Phenotyping

A secondary endpoint of the study will be the incidence of observed genotypic and phenotypic resistance to DTG or 3TC and to current ART for participants meeting Virologic Withdrawal criteria. The virologic endpoint may also be assessed based on third-agent class.

9.5.2. HIV-1 Exploratory Analyses

To assess the future drug options in participants meeting confirmed virologic failure criteria, drugs potentially impacted and remaining available for participants with treatment emergent resistance will be evaluated.

After meeting virologic withdrawal criteria, additional analyses for HIV-1 resistance may, for example, be carried out on peripheral blood mononuclear cell (whole blood) samples collected at Baseline and/or on stored plasma samples from other relevant time points. These analyses may include but are not limited to additional viral genotyping and/or phenotyping, as well as other virologic evaluations such as linkage and minority species analyses, low level HIV-1 RNA quantitation and measurement of viral replicative capacity. HIV-1 PR and RT genotype and phenotype and HIV-1 integrase genotype and phenotype will also be determined on the last on-treatment isolates from participants who have HIV-1 RNA ≥400 c/mL regardless of confirmatory HIV-1 RNA.

9.6. Pharmacokinetics

9.6.1. Blood Sample Collection

- Serial (intensive) and sparse blood samples will be collected for measurement of plasma concentrations of DTG at the time points specified in the SoA (Section 2) and in Section 9.6.2.3. The date and time of dosing and actual date and time of each blood sample collection will be recorded.
- Samples will be used to evaluate the plasma PK of DTG and 3TC. For each time point identified in SoA, approximately 2 mL of blood will be collected into di-potassium ethylenediaminetetraacetic acid (K2EDTA) tubes. Details of PK blood sample collection, processing, storage and shipping procedures are provided in the Investigator site file.
- Genetic analyses will not be performed on these blood samples. Participant confidentiality will be maintained.

9.6.1.1. Collection of Sparse PK samples – All Participants

Table 2 Pharmacokinetic Sparse Sample Schedule

Week	Sample Times Relative to Dose
4	1 pre-dose[a] sample AND 1 sample 2 to 4 hr post dose[b]
12	1 pre-dose sample[a] AND 1 sample 4 to 12 hr post dose[b]
24	1 pre-dose sample[a] AND 1 sample 12 to 24 hr post dose [b]

a. Pre-dose samples will be collected immediately before the dose (i.e. within 15 minutes) which will be taken under observation at the clinic. Pre-dose samples should be collected 20-28 hours post previous dose.

b. All sample timepoints must be obtained from each participant. These samples may be drawn at any time during the specified interval.

Note: Participants are to complete a dosing diary card for 3 days prior to PK sampling visit. The PK visit should be re-scheduled if the participant took their morning dose prior to coming into the clinic on the PK sampling day.

9.6.1.2. Collection of Ctrough samples- All Participants

A single sample for analysis of Ctrough will be collected at other clinical visits (i.e. Weeks 8, 16, 36, and 48). These samples will be collected immediately prior to dosing which will be taken under observation at the clinic.

9.6.2. Important Information on collection of PK samples

It is important to collect PK samples according to the specified procedure and timeline.

9.6.2.1. Timing of sparse PK sample collection

Flexibility is allowed in collecting the post-dose samples (anywhere from 2 to 4 hours and 12 to 24 hours post dose) to accommodate participant schedules and so that a range of sample times can be obtained. Participants may choose to remain in clinic until 2 to 4 hours after taking study medication. Also, to allow flexibility in scheduling PK draws while maintaining quality and accuracy, the week 4, week 12, week 24 samples can be drawn interchangeably (i.e. 2 to 4 hours post-dose drawn at week 12 and the 4 to 12 hours post-dose drawn at week 4) as long as all three samples (2 to 4 hours, 4 to 12 hours, and 12 to 24 hours post-dose) are obtained for each participant.

9.6.2.2. Dosing Diary Cards

To enhance the quality of Ctrough, sparse and intensive PK data collection, participants will be asked to complete a dosing diary card with the following information which will be included in eCRF:

- The date and time of the DTG/3TC FDC administration for 3 days prior to the scheduled Ctough, sparse or intensive PK clinic visit;
- Whether or not the doses were taken with a meal;
- Whether or not the subject vomited within 4 hours of taking the study drug

Three days prior to the scheduled Ctrough, sparse or intensive PK visits, the site personnel will contact the participant to remind them:

- When their next visit is scheduled, time to arrive at the site and any other practical information and instructions with regard to the PK sampling;
- To complete all sections of the dosing card for 3 days prior to the visit;
- No doses can be missed during the 3 days prior to the scheduled PK visit;
- Not take a dose of IP before the clinic visit so that a pre-dose sample can be drawn before that days DTG/3TC FDC dose

If a participant presents at clinic for a pre-dose PK sample collection having already taken the morning dose or having missed doses within the previous 3 days, it is recommended to reschedule PK sampling at the next clinic visit or an ad hoc clinic visit for this purpose. It is not recommended to collect PK samples if date and time of dosing for the previous 3 days cannot be reliably confirmed.

9.6.2.3. Collection of Intensive Serial PK samples

Intensive serial PK samples will be collected in a subset of approximately 12 participants to ensure data from 10 evaluable participants at selected sites. Serial PK sampling should be scheduled between Days 5 and 10. Flexibility is allowed in scheduling serial PK collection to accommodate participants' schedules.

Additional details on sample collection in this subset of participants is provided in the Investigator site file.

Table 3 Pharmacokinetic Serial Intensive Sample Schedule

Day	Sample Times Relative to Dose
5 to 10	Pre-dose[a], 0.5, 1.0, 1.5, 2, 3, 4, 6, 10, and 24[b] hours post dose

a. Pre-dose samples will be collected immediately before the dose (i.e. within 15 minutes) which will be taken under observation at the clinic.
b. Participants in the intensive PK sampling group must return to the site the next morning for the 24-hour post dose blood sample collection.

9.6.3. Sample Analysis

Plasma analysis will be under the control of Platform Technology Services (PTS) PTS GlaxoSmithKline, the details of which are provided in the Investigator site file. Concentrations of DTG and 3TC will be determined in plasma samples using he currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the Investigator site file).

Analysis of the PK data collected is explained in detail in Section 10.3.3

9.7. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.8. Genetics

Genetics are not evaluated in this study.

9.9. Biomarkers

Biomarkers are not evaluated in this study.

9.10. Health Economics

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

10. STATISTICAL CONSIDERATIONS

10.1. Sample Size Determination

This study will enroll 30 adolescent participants and is proposed to complement the fully powered non-inferiority evaluation of the DTG/3TC combination performed in adults. The reported Week 48 response rates for DTG+2NRTIs in adults are 88% to 90% (ITT-E, % <50 c/mL by Snapshot algorithm). It is therefore reasonable to conservatively

expect a lower response rate of 77% (23/30) or 80% (24/30) in adolescents based on their recognized treatment adherence difficulties.

A single arm study with 30 participants will provide an exact Clopper Pearson 95% CI of 61%-92% for an assumed response rate of 80% (% <50 c/mL by Snapshot algorithm at Week 48). The study will provide an exact Clopper Pearson 95% CI of 58%-90% if the assumed response rate is 77% (% <50 c/mL by Snapshot algorithm at Week 48).

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

10.2.1. Intent-to-Treat Exposed (ITT-E) Population

This population will consist of all enrolled participants who receive at least one dose of study medication. Unless stated otherwise, the ITT-E Population will be used for efficacy analyses.

10.2.2. Per Protocol (PP) Population

This population will consist of participants in the ITT-E Population with the exception of major protocol violators: e.g., violations which could affect the assessment of antiviral activity; this will be defined in the RAP. The PP population will be used for sensitivity analyses of the primary efficacy measure.

10.2.3. Safety Population

The Safety Population is defined as all participants who receive at least one dose of study medication. Participants will be analyzed according to the actual treatments received. Unless otherwise stated, the Safety Population will be used for safety analyses.

10.2.4. Pharmacokinetic Populations

Sparse PK population is defined as all participants who received at least 1 dose of DTG/3TC and have evaluable sparse samples with drug concentrations reported.

Intensive PK population is defined as the subset of participants enrolled into intensive PK sampling, who received at least 1 dose of DTG/3TC and have evaluable drug concentrations reported.

The defining of evaluable drug concentrations and further details on the PK populations will be described in the reporting and analysis plan (RAP).

10.2.5. Analysis Data Sets

The primary analysis set of data is based on virologic failure and success as defined by the FDA snapshot MSDF (Missing, Switch of Discontinuation = Failure) algorithm. With

the exception below, virologic failure includes participants who changed any component of background therapy to a new drug class, changed background components that were not permitted per protocol, or changed any background drug in the regimen because of lack of efficacy (perceived or documented) before Week 48; patients who discontinued study drug or study before Week 48 for lack or loss of efficacy and patients who are equal to or above 50 c/mL in the 48-week window. This will also be reported by study visit. This algorithm treats all participants without HIV-1 RNA data at the visit of interest (due to missing data or discontinuation of IP prior to visit window) as non-responders, as well as participants who switch their concomitant ART prior to the visit of interest, since no switches (with the exception below) are allowed in the protocol.

Otherwise, virologic success or failure will be determined by the last available HIV-1 RNA assessment while the participant is on-treatment within the visit of interest window (to be specified in the RAP). Full details of this snapshot algorithm will be contained in the RAP.

Another secondary set of data will treat participants as censored if they discontinue for reasons other than those related to treatment (AEs, tolerability and lack of efficacy). This data set will be the Treatment Related Discontinuation = Failure (TRDF) data set.

The observed case (OC) dataset, which uses only data that are available at a particular time point with no imputation for missing values, will be the primary dataset for assessing safety and will also be used for some analyses of efficacy.

Further details will be provided in the RAP.

10.3. Statistical Analyses

10.3.1. Efficacy Analyses

All efficacy analyses will be performed on the IIT-E and per protocol populations.

The primary endpoint of the proportions of participants meeting the criteria for virologic success as defined by the FDA snapshot algorithm will be reported with exact Clopper Pearson 95% confidence intervals.

Change in CD4/8 count and percent from baseline to weeks 24 and 48 will be bounded by 95% confidence intervals.

Further details including details on the week 96 and 144 analyses will be provided in the RAP.

10.3.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Exposure to study medication, measured by the number of weeks on study drug, will be summarized. The proportion of participants reporting AEs will be tabulated. The following summaries of AEs will be provided:

- Incidence and severity of all AEs
- Incidence and severity of treatment related AEs
- Incidence and severity of AEs leading to withdrawal
- Incidence of SAEs
- Cumulative incidence of AEs by time to first occurrence
- Cumulative incidence of treatment related AEs by time to first occurrence

Laboratory data will be summarized by visit. In addition, the number and percentage of participants with graded laboratory toxicities (based on Division of AIDS [DAIDS] categories) will be summarized. The proportion of participants experiencing changes from Baseline in their National Cholesterol Education Program (NCEP) lipid categories will be summarized. Further details of safety analyses will be included in the RAP.

10.3.3. Pharmacokinetic Analyses

10.3.3.1. Intensive Pharmacokinetic Analyses

PK analyses will be the responsibility of Clinical Pharmacology Modeling and Simulation department within GSK or their designee.

For participants participating in serial sampling, plasma DTG and 3TC concentration-time data will be analyzed by non-compartmental methods with Phoenix WinNonlin version 4.1 or higher. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following pharmacokinetics parameters will be determined as data permit:

- Maximum observed plasma concentration (Cmax)
- Time of maximum observed plasma concentration (tmax)
- Area under the plasma concentration-time curve [AUC from time zero (pre-dose) to last time of quantifiable concentration, AUC(0-t) and AUC over the dosing interval, AUC(0-τ)]
- Apparent terminal half-life ($t_{1/2}$)
- Observed pre-dose (trough) concentration (C0)
- Observed plasma concentration at the end of a dosing interval (e.g. concentration at 24 hours) (C24)

Any additional PK parameters that are calculated will be provided in the RAP.

Results based on samples collected from a participant with emesis within 4 hours of the dose will not be considered.

All PK data will be stored in the R&D archives, GSK.

Statistical analyses of the PK parameter data will be the responsibility of the study sponsor and/or its delegate services provider. Details of the statistical analysis will be provided in the RAP. An outline is provided below:

PK data will be presented in graphical and tabular form and will be summarized descriptively. Plasma DTG concentration-time data will be listed by participant and time point and summarized descriptively at each time point. Individual participant profiles for DTG concentration-time data will be presented on both a linear and semi-log scale. Plots on the linear and semi-log scale for mean and median DTG plasma concentrations versus time will also be generated. Plasma DTG parameters will be log-transformed prior to analysis.

10.3.3.2. Sparse Pharmacokinetic Analysis

Sparse plasma concentration-time data collected in all participants may be combined with serial data and pooled with data from other studies to perform an integrated population PK analysis. Further details of the population PK analysis will be provided in the RAP. If performed, this analysis will be reported separately.

10.3.4. Other Analyses

All other analyses will be described in the reporting and analysis plan.

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

10.3.5. Secondary Analyses

At least three analyses will be conducted to evaluate primary and secondary objectives of the protocol, one when all subjects have completed their visits at Week 48, at Week 96, and at Week 144. Further data cuts and analyses may be conducted as necessary after Week 144, in the Continuation Phase, to support regulatory submissions and publications.

The Week 48 analysis will be primary. No adjustment for multiplicity caused by repeated evaluation of the primary endpoint will be made as the Week 96, and Week 144 analyses will be secondary.

An IDMC will be instituted to ensure external objective medical and/or statistical review of efficacy and safety in order to protect the ethical interests and well-being of subjects and to protect the scientific validity of this study. An initial IDMC data look will occur after 3 participants complete the Week 12 visit. Subsequent meetings will occur approximately once every 6 months with potential for additional ad-hoc meetings. Ad-hoc reviews of data by the IDMC may be triggered whenever the number of CVWs

exceeds thresholds pre-specified in the IDMC charter. Full details of the methods, timing, decision criteria and operating characteristics will be pre-specified in the IDMC Charter.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

3TC	Lamivudine, EPIVIR
ABC	Abacavir, ZIAGEN
ABC/3TC	Abacavir/lamivudine, EPZICOM, KIVEXA
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
Anti-HBc	Hepatitis B core antibody
Anti-HBs	Hepatitis B surface antibody
ARV	Antiretroviral
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
AUC	Area Under the Curve
B	Baseline
C	Continuation phase
CDC	Centers for Disease Control and Prevention
cm	Centimeter
CMO	Chief Medical Officer
COVID-19	Coronavirus Disease 2019
CrCl	Creatinine clearance
CRF	Case report form
CVW	Confirmed virologic withdrawal
DAIDS	Division of Acquired Immunodeficiency Syndrome
DNA	Deoxyribonucleic acid
DTG	Dolutegravir, TIVICAY
DTG/3TC	Dolutegravir/lamivudine, DOVATO
dL	Deciliter
E	Extension Phase Visit
EC	End of Continuation Phase Visit
ECG	Electrocardiogram
eCRF	electronic Case report form
eC-SSRS	electronic Columbia Suicidality Severity Rating Scale
EU	European Union
F	Follow-up Visit
FDA	Food and Drug Administration
FDC	Fixed-dose combination
FRP	Females of reproductive potential
GCP	Good clinical practice
eGFR	Estimated Glomerular filtration rate
GSK	GlaxoSmithKline
Hb1Ac	Glycated hemoglobin

HBsAb	Hepatitis B surface antibody
(anti)-HBc	Hepatitis B core antibody
HBV	Hepatitis B virus
hCG	Human chorionic gonadotrophin
HCV	Hepatitis C virus
IDMC	Independent data monitoring committee
IN	Integrase
INR	International normalized ratio
INSTI	Integrase strand transfer inhibitor
ITT	Intent to treat
IVRS/IWRS	Interactive voice/web response system
mL	Milliliter
Min	Minute
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
PEP	Post-exposure prophylaxis
PrEP	Pre-exposure prophylaxis
PI	Protease inhibitor
PK	Pharmacokinetic
PMTCT	Prevention of mother to child transmission
PPD	Pharmaceutical Product Development
PR	Protease
RAL	Raltegravir
RAP	Reporting and analysis plan
RNA	Ribonucleic acid
RPR	Rapid plasma reagin
RT	Reverse transcriptase
RTV	Ritonavir
SAE	Serious adverse event
SC	Screening Visit
STR	Single tablet regimen
SVW	Suspected virologic withdrawal
TDF/FTC	Tenofovir disoproxil fumarate/ emtricitabine
ULN	Upper limit of normal
VSLC	ViiV Healthcare safety and labelling committee
W	Withdrawal Visit
WHO	World Health Organization
ZDV	Zidovudine, RETROVIR
ZDV/3TC	Zidovudine/lamivudine, COMBIVIR

Trademark Information

Trademarks of the ViiV Healthcare group of companies
COMBIVIR
DOVATO
EPIVIR
EPZICOM
KIVEXA
TIVICAY
TRIZIVIR

Trademarks not owned by the ViiV Healthcare group of companies
GenoSure
MedDRA
PhenoSense
WinNonlin

12.2. Appendix 2: Child-Pugh Classification

A participant is classified with mild hepatic impairment (Class A) if their overall sum of scores is CCI points, moderate hepatic impairment (Class B) if their overall sum of scores is CCI points, and severe hepatic impairment (Class C) if their overall sum of scores is CCI CCI based on the Child-Pugh system [Pugh, 1973] scoring described in the following table (Table 4). For participants requiring anticoagulation therapy, discussion with the study Medical Monitor will be required.

Table 4 Child-Pugh System

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

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12.3. Appendix 3: Liver Safety Required Actions and Follow up Assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria - Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td>ALT ≥ 8xULN</td></tr>
<tr><td>ALT Increase</td><td>ALT ≥ 5xULN but <8xULN persists for ≥2 weeks (with bilirubin <2xULN and no signs or symptoms of acute hepatitis or hypersensitivity)</td></tr>
<tr><td>Bilirubin[1, 2]</td><td>ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin)</td></tr>
<tr><td>INR2</td><td>ALT ≥ 3xULN and INR>1.5, if INR measured</td></tr>
<tr><td>Cannot Monitor</td><td>ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for >2 weeks</td></tr>
<tr><td>Symptomatic[3]</td><td>ALT ≥ 3xULN (if baseline ALT is ≤ULN) with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

ALT ≥3xbaseline (if baseline ALT>ULN) with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="2">Required Actions and Follow up Assessments following ANY Liver Stopping Event</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study treatment.
• Report the event to the Medical Monitor within 24 hours.
• Complete the liver event eCRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2].
• Complete the liver imaging and/or liver biopsy eCRFs if these tests are performed.
• Perform liver event follow up assessments.
• Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below).
• Do not restart participant with study treatment unless allowed per protocol and VSLC approval is granted (refer to Appendix 5, Section 12.5– Liver Safety – Study Treatment Restart of Rechallenge Guidelines).</td><td>• Viral hepatitis serology, including:
  • Hepatitis A immunoglobulin M (IgM) antibody;
  • HBsAg and hepatitis B core antibody;
  • Hepatitis C RNA;
  • Hepatitis E IgM antibody.
• Cytomegalovirus IgM antibody.
• Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing).
• Syphilis screening.
• Drugs of abuse screen, including alcohol. Record alcohol use on the liver event eCRF
• Serum acetaminophen adduct HPLC assay (quantifies potential</td></tr>
</table>

• If restart is **not allowed or not granted**, permanently discontinue study treatment and may continue participant in the study for any protocol specified follow up assessments. **MONITORING:** • Make every reasonable attempt to have participants return to clinic within **24 hours** for repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments (at the central laboratory) as described to the right. • Monitor participants twice weekly until liver chemistries resolve, stabilise or return to within baseline. • A specialist or hepatology consultation is recommended.	acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). The site must contact the Medical Monitor when this test is required. • Blood sample for pharmacokinetic (PK) analysis, obtained within 60 hours of last dose[4]. • Serum CPK and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin ≥1.5xULN. • Obtain complete blood count with differential to assess eosinophilia. • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms. • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash as relevant on the AE report form.

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) **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. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia).
4. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the Investigator site file

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for >2 weeks.	• Notify the Medical Monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study treatment • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until resolution, stabilisation (ALT <5×ULN on 2 consecutive evaluations) or return to within baseline • If at any time participant meets the liver chemistry stopping criteria, proceed as described above

12.4. Appendix 4: Study Governance Considerations

12.4.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of participants begins.

12.4.2. Regulatory and Ethical 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 (eg, 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.

12.4.3. Informed Consent and Assent Process

- The investigator or his/her representative will explain the nature of the study to the participant and his/her legally authorized guardian.

- Participants must be informed that their participation is voluntary. Each participant's legally authorized guardian (or the participant as required by local law) 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 center.

- Where appropriate, participants must also provide written assent for participation in the study. The written assent form will meet 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 center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

- As participants meet what is considered the age of majority in the country (e.g. 18 years of age), they must sign the currently approved informed consent form to continue in the study.

- A copy of the ICF(s) must be provided to the participant and the participant's legally authorized guardian.

- Participants who are rescreened or who restart study medication after temporarily stopping for toxicity management are required to sign a new ICF.

The informed consent process will include information exchange, detailed discussion, and assessment of understanding of all required elements of informed consent, including the potential risks, benefits, and alternatives to study participation. Written informed consent must be obtained from the participant (or parents or legal guardians of participants who cannot consent for themselves, such as those below the legal age). The participant's assent must also be obtained if he or she is able to understand the nature, significance, and risks of the study. The informed consent will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the participant (or parent or legal guardian).

It is generally expected that only one parent or legal guardian will provide informed consent for the child's participation in this study. However, parental consenting requirements at each site will depend on the IRB/IEC risk determination.

Should the parent or legal guardian of an enrolled child die or no longer be available for any reason, no further study-specific visits or procedures may be performed until informed consent for continued study participation is obtained from a locally authorized guardian. Study sites should establish and maintain written procedures describing the standards that will be followed to identify who may serve as guardian for an enrolled adolescent, reflective of applicable IRB/IEC guidance for conduct of human participants research within the context of available local law, regulation, or government policy.

Children who are wards of State or any other agency, institution or entity are excluded from enrollment into this study. The site Investigator must notify the Study Medical Monitor immediately if a participant's guardianship status changes such that they become a ward during the study. If this occurs, the ViiV Chief Medical Officer must determine if the participant may continue in the study.

12.4.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/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.

12.4.5. Independent Data Monitoring Committee

Because a dual regimen of DTG/3TC represents a new treatment paradigm for HIV infection, an IDMC will be used in this study to ensure external objective medical and/or statistical review of safety and/or efficacy issues in order to protect the ethical and safety interests of participants and to protect the scientific validity of this study. The schedule of the analysis plan for IDMC review is described in the IDMC charter, which is available upon request.

All communications received from the IDMC regarding the status of the study will be shared with investigators in a timely manner.

12.4.6. Dissemination and Publication of Clinical Study Data

12.4.6.1. Dissemination of 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/GSK site or other mutually-agreeable location.

ViiV Healthcare/GSK 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/GSK Policy.

12.4.6.2. Publication of Study Data

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

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

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

12.4.7. Data Quality Assurance and Control

12.4.7.1. 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 (eg, 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. To ensure compliance with GCP and all applicable regulatory requirements, ViiV Healthcare/GSK/PPD may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.

In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

12.4.7.2. Quality Control

The sponsor or designee is responsible for the data management of this study including quality checking of the data. The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

In accordance with applicable regulations including GCP, and PPD procedures, PPD monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and ViiV Healthcare, GSK or PPD requirements.

When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

PPD will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of participants are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

12.4.8. Source Documents and Retention

12.4.8.1. 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.

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, 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 eCRF. Data reported on the eCRF 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.

12.4.8.2. Records Retention

Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.

The records must be maintained to allow easy and timely retrieval, when needed (e.g. for a ViiV Healthcare/GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.

The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

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.

The investigator must notify ViiV Healthcare, GSK or PPD of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

12.4.9. Study and Site Closure

Upon completion or premature discontinuation of the study, the PPD monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and PPD Standard Operating Procedures.

ViiV Healthcare/GSK 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/GSK. For multicenter studies, this can occur at one or more or at all sites. Reasons for early closure of a study may include safety or ethical issues or severe non-compliance. Reasons for 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

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.

12.5. Appendix 5: Liver Safety – Study Treatment Restart or Rechallenge Guidelines

If a participant meets liver chemistry stopping criteria, do not restart/rechallenge participant with study treatment unless:

- ViiV Healthcare Safety and Labelling Committee (VSLC) approval **is granted**
- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for treatment restart/rechallenge is signed by the participant

If VSLC approval to restart/rechallenge participant with study treatment **is not granted**, then participant must permanently discontinue study treatment and may continue in the study for protocol-specified follow up assessments.

12.5.1. Drug Rechallenge Following Liver Events that are Possibly Related to IP

Following drug-induced liver injury, **drug rechallenge is associated with a 13% mortality across all drugs in prospective studies** [Andrade, 2009]. Clinical outcomes vary by drug, with nearly 50% fatality with halothane readministered within one month of initial injury. However, some drugs seldom result in recurrent liver injury or fatality.

Risk factors for a fatal drug rechallenge outcome include:

- Hypersensitivity [Andrade, 2009] with initial liver injury (e.g. fever, rash, eosinophilia)
- jaundice or bilirubin >2xULN with initial liver injury (direct bilirubin >35% of total)
- participant currently exhibits severe liver injury defined by: ALT ≥3xULN, bilirubin ≥2xULN (direct bilirubin >35% of total), or INR≥1.5
- serious adverse event or fatality has earlier been observed with drug rechallenges [Hunt, 2010; Papay, 2009]
- evidence of drug-related preclinical liability (e.g. reactive metabolites; mitochondrial impairment [Hunt, 2010].

Rechallenge refers to resuming study treatment following drug induced liver injury (DILI). Because of the risks associated with rechallenge after DILI this should only be considered for a participant for whom there is compelling evidence of benefit from a critical or life-saving medicine, there is no alternative approved medicine available, and a benefit:risk assessment of rechallenge is considered to be favourable.

Approval by the VSLC for drug rechallenge can be considered where:

- Principal Investigator (PI) requests consideration of rechallenge with study treatment for a participant is receiving compelling benefit, benefit of drug restart exceeds risk, and no effective alternative therapy is available. Ethics Committee

or Institutional Review Board approval of drug restart/rechallenge must be obtained, as required.

- If the restart/rechallenge is approved by the VSLC in writing, the participant must be provided with a clear description of the possible benefits and risks of drug administration, including the possibility of recurrent, more severe liver injury or death.
- The participant must also provide signed informed consent specifically for the IP restart/rechallenge. Documentation of informed consent must be recorded in the study chart.
- Study drug must be administered at the dose specified by the VSLC.
- Participants approved by the VSLC for rechallenge of IP must return to the clinic twice a week for liver chemistry tests for a minimum of one month and thereafter for as long as clinically indicated and then laboratory monitoring may resume as per protocol.
- If after study treatment rechallenge, participant meets protocol defined liver chemistry stopping criteria, study drug must be permanently discontinued.
- The Medical Monitor and the Ethics Committee or Institutional Review Board as required, must be informed of the participant's outcome following study treatment rechallenge
- Any adverse events should be recorded on the appropriate eCRF(s), and reported where applicable, as per Section 9.3.1.1.

12.5.2. Drug Restart Following Transient Resolving Liver Events Not Related to IP

Restart refers to resuming study treatment following liver stopping events in which there is a clear underlying cause (other than DILI) of the liver event (e.g. biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the study treatment should not be associated with HLA markers of liver injury.

Approval by the VSLC for drug restart can be considered where:

- Investigator requests consideration for study treatment restart if Liver chemistries have a clear underlying cause (e.g., biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5 x baseline and ALT <5xULN).
- Furthermore, there should be no evidence of fever, rash, eosinophilia, hypersensitivity, alcoholic hepatitis or possible study treatment-induced liver, and the drug should not be associated with HLA markers of liver injury. (If restart of TRIUMEQ or any other abacavir- containing product is being considered then the Participant must be HLA-B*5701 negative).
- Ethics Committee or Institutional Review Board approval of drug restart/rechallenge must be obtained, as required.

- If restart of drug is approved by the VSLC in writing, the participant must be provided with a clear description of the possible benefits and risks of drug administration, including the possibility of recurrent, more severe liver injury or death.
- The participant must also provide signed informed consent specifically for the restart. Documentation of informed consent must be recorded in the study chart.
- Study drug must be administered at the dose specified by the VSLC.
- Participants approved by the VSLC for restarting IP must return to the clinic once a week for liver chemistry tests for a minimum of one month and thereafter for as long as clinically indicated and then laboratory monitoring may resume as per protocol.
- If after study treatment re-start, participant meets protocol-defined liver chemistry stopping criteria, follow usual stopping criteria instructions.
- The Medical Monitor and the Ethics Committee or Institutional Review Board as required, must be informed of the participant's outcome following study treatment restart
- Any adverse events should be recorded on the appropriate eCRF(s), and reported where applicable, as per Section 9.3.1.1.

References:

Andrade RJ, Robles M, Lucena MI. Rechallenge in drug-induced liver injury: the attractive hazard. Expert Opin Drug Saf. 2009;8:709-714.

Hunt, CM. Mitochondrial and immunoallergic injury increase risk of positive drug rechallenge after drug-induced liver injury: A systematic review. Hepatol. 2010;52:2216-2222.

Papay JI, Clines D, Rafi R, Yuen N, Britt SD, Walsh JS, Hunt CM. Drug-induced liver injury following positive drug rechallenge. Regul Tox Pharm. 2009;54:84-90.

12.6. Appendix 6: CDC Classification and WHO Staging for HIV-1 Infection

12.6.1. CDC Classification for HIV-1 Infection

Note that the CD4+ T-lymphocyte count takes precedence over the CD4+ T-lymphocyte percentage in HIV infection stages 1, 2, and 3. The CD4+ T-lymphocyte percentage should only be considered if the count is missing.

HIV infection, stage 0

Indicates early HIV infection, inferred from a negative or indeterminate HIV test result within 180 days of a positive result. The criteria for stage 0 supersede and are independent of criteria used for other stages.

HIV infection, stage 1

- Laboratory confirmation of HIV infection with no AIDS-defining condition, and
    - CD4+ T-lymphocyte count of ≥500 cells/μL, or
    - CD4+ T-lymphocyte percentage of total lymphocytes of ≥26%.

HIV infection, stage 2

- Laboratory confirmation of HIV infection with no AIDS-defining condition, and
    - CD4+ T-lymphocyte count of 200 to 499 cells/μL, or
    - CD4+ T-lymphocyte percentage of total lymphocytes of 14% to 25%.

HIV infection, stage 3 (AIDS)

- Laboratory confirmation of HIV infection, and
    - CD4+ T-lymphocyte count of <200 cells/μL, or
    - CD4+ T-lymphocyte percentage of total lymphocytes of <14%, or
    - Documentation of an AIDS-defining condition (see below).

Documentation of an AIDS-defining condition supersedes a CD4+ T-lymphocyte count of >200 cells/μL and a CD4+ T-lymphocyte percentage of total lymphocytes of >14%.

HIV infection, stage unknown

- Laboratory confirmation of HIV infection, and
    - No information on CD4+ T-lymphocyte count or percentage, and
    - No information on presence of AIDS-defining conditions.

Category C-defining opportunistic illnesses in HIV infection

- Candidiasis of bronchi, trachea, or lungs

- Candidiasis of oesophagus
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or oesophagitis (onset at age >1 month)
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month's duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- Mycobacterium avium complex or Mycobacterium kansasii, disseminated or extrapulmonary
- Mycobacterium tuberculosis of any site, pulmonary, disseminated or extrapulmonary
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- Pneumocystis jirovecii pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- Salmonella septicaemia, recurrent
- Toxoplasmosis of brain, onset at age >1 month
- Wasting syndrome attributed to HIV.

Reference:

Centers for Disease Control and Prevention. *1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults*. MMWR Recomm Rep. 1992 Dec 18;41(RR-17):1-19. Available at: https://www.cdc.gov/mmwr/preview/mmwrhtml/00018871.htm. Accessed December 4, 2017.

12.6.2. World Health Organization. WHO Classification of HIV-Related Disease in Adults and Adolescents

Clinical Stage 1

- Asymptomatic

Persistent generalized lymphadenopathy

Clinical Stage 2

- Moderate unexplained weight loss (<10% of presumed or measured body weight)[a]
- Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media and pharyngitis)
- Herpes zoster
- Angular cheilitis
- Recurrent oral ulceration
- Papular pruritic eruptions
- Seborrhoeic dermatitis
- Fungal nail infection

Clinical Stage 3

- Unexplained[b] severe weight loss (>10% of presumed of measured body weight)
- Unexplained chronic diarrhoea for longer than one month
- Unexplained persistent fever (above 36.7°C intermittent or constant for longer than one month)
- Persistent oral candidiasis
- Oral hairy leukoplakia
- Pulmonary tuberculosis (current)
- Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis or bacteraemia)
- Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
- Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 x 109 per litre) or chronic thrombocytopaenia (<50 x 109 per litre)

Clinical Stage 4[c]

- HIV wasting syndrome
- Pneumocystis pneumonia

- Recurrent sever bacterial pneumonia
- Chronic herpes simplex infection (orolabial, genial or anorectal of more than one month's duration or visceral at any site)
- Oesophageal candidiasis (or candidiasis or trachea, bronchi or lungs)
- Extrapulmonary tuberculosis
- Kaposi's sarcoma
- Cytomegalovirus infection (retinitis or infection of other organs)
- Central nerous system toxoplasmosis
- HIV encephalopathy
- Extrapulmonary cryptococcosis including meningitis
- Disseminate non-tuberculous mycobacterial infection
- Progressive multifocal leukoencephalopathy
- Chronic cryptosporidiosis (with diarrhoea)
- Chronic isosporiasis
- Disseminated mycosis (coccidiomycosis or histoplasmosis)
- Recurrent non-typhoidal Salmonella bacteraemia
- Lymphoma (cerebral or B-cell non-Hodgkin) or other solid HIV-associated tumours
- Invasive cervical carcinoma
- Atypical disseminated leishmaniasis
- Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy

[a] Assessment of body weight in pregnant woman needs to consider the expected weight gain of pregnancy

[b] Unexplained refers to where the condition Is not explained by other causes

[c] Some additional specific conditions can also be included in regional classifications (such as reactivation of American trypanosomiasis [meningoencephalitis and/or myocarditis]) in the WHO Region of the Americas and disseminated penicilliosis in Asia).

Reference:

World Health Organization. *WHO Case Definitions of HIV for Surveillance and Revised Clinical Staging and Immunological Classification of HIV-Related Disease in Adults and Children*. 2007. Available at: http://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf?ua=1. Accessed December 4, 2017.

12.7. Appendix 7: Division of AIDS Table for Grading Severity of Adults and Pediatric Adverse Events

VERSION 2.1, March 2017

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

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

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

Major Clinical Conditions Cardiovascular

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Cardiovascular

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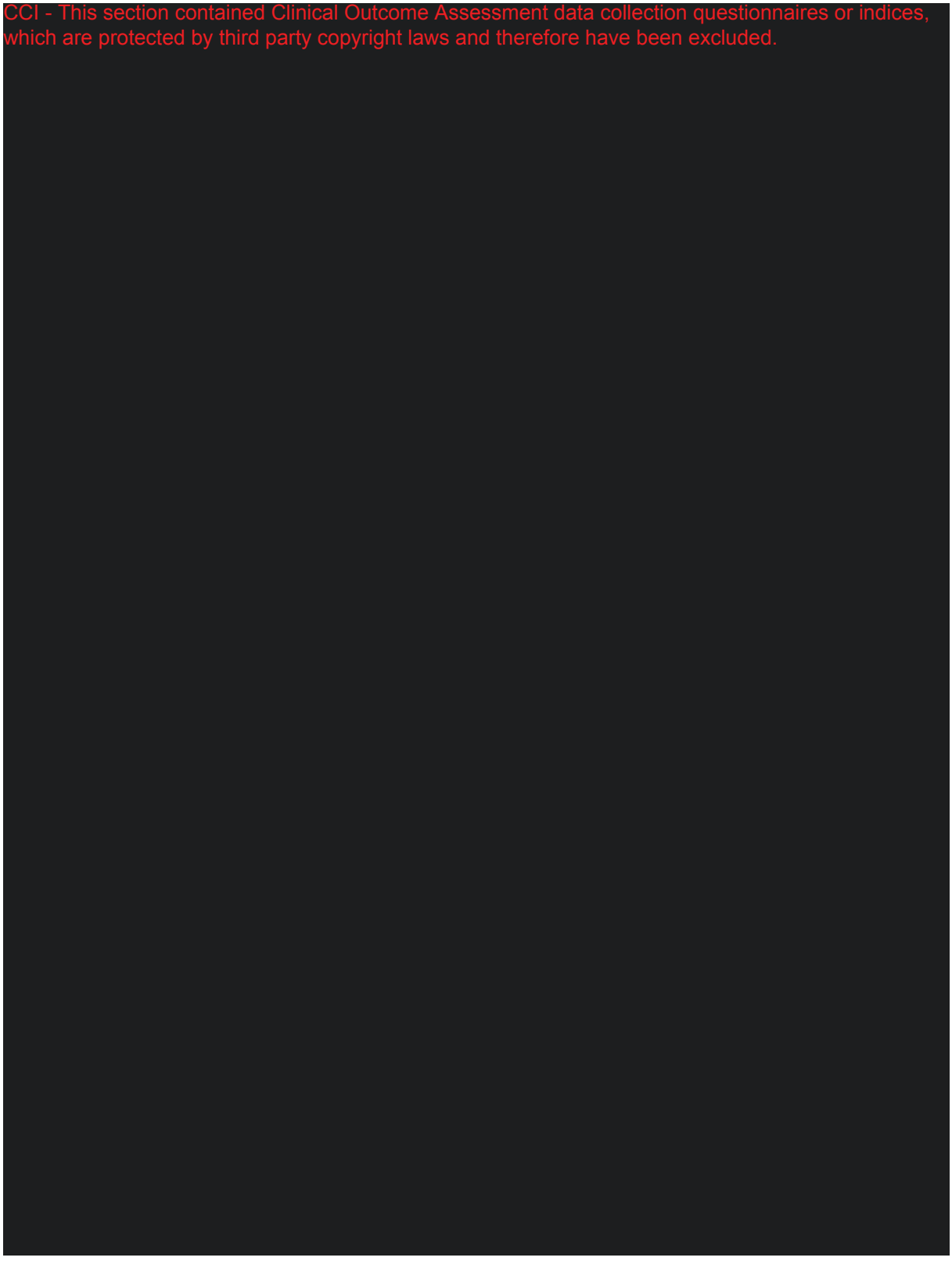
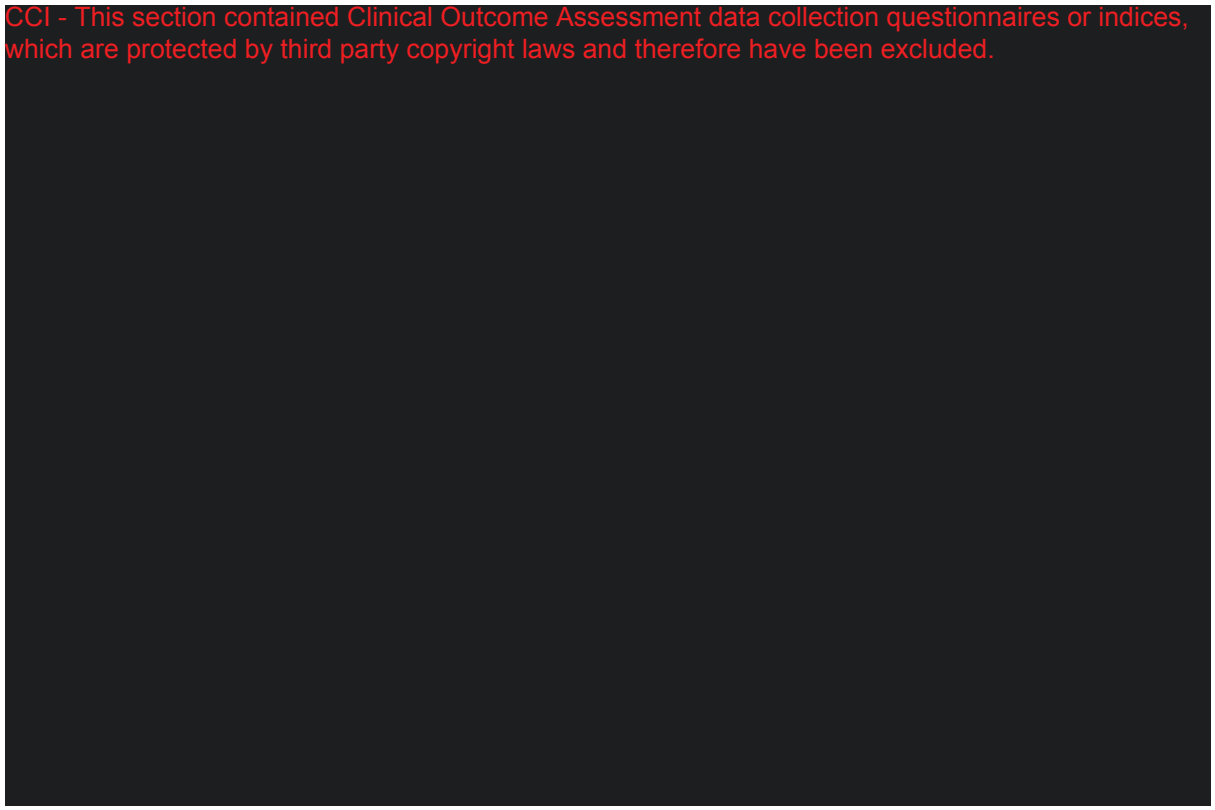
Dermatologic



Endocrine and Metabolic



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Gastrointestinal

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Musculoskeletal

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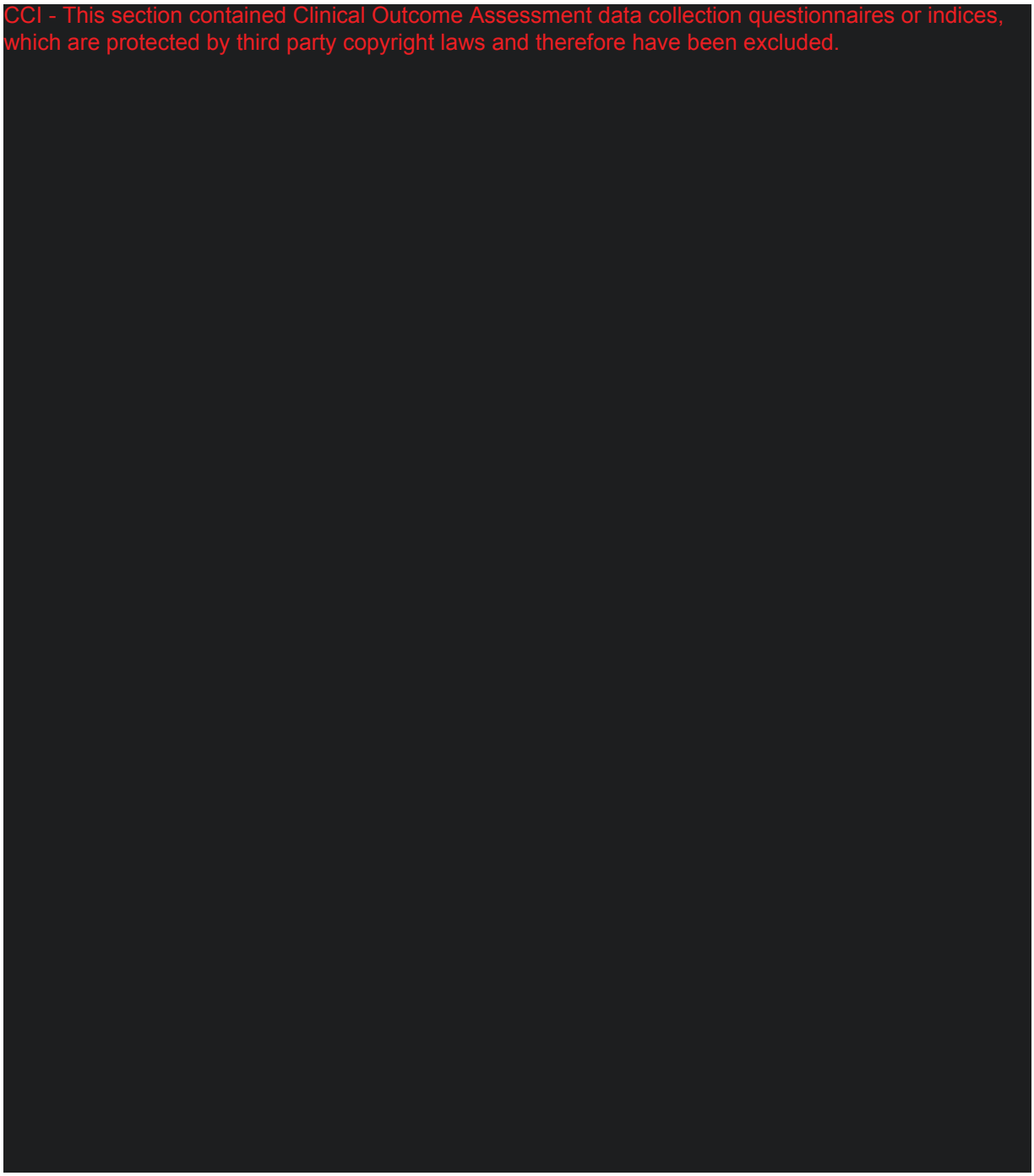
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Neurologic

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Pregnancy, Puerperium, and Perinatal

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Psychiatric

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Respiratory

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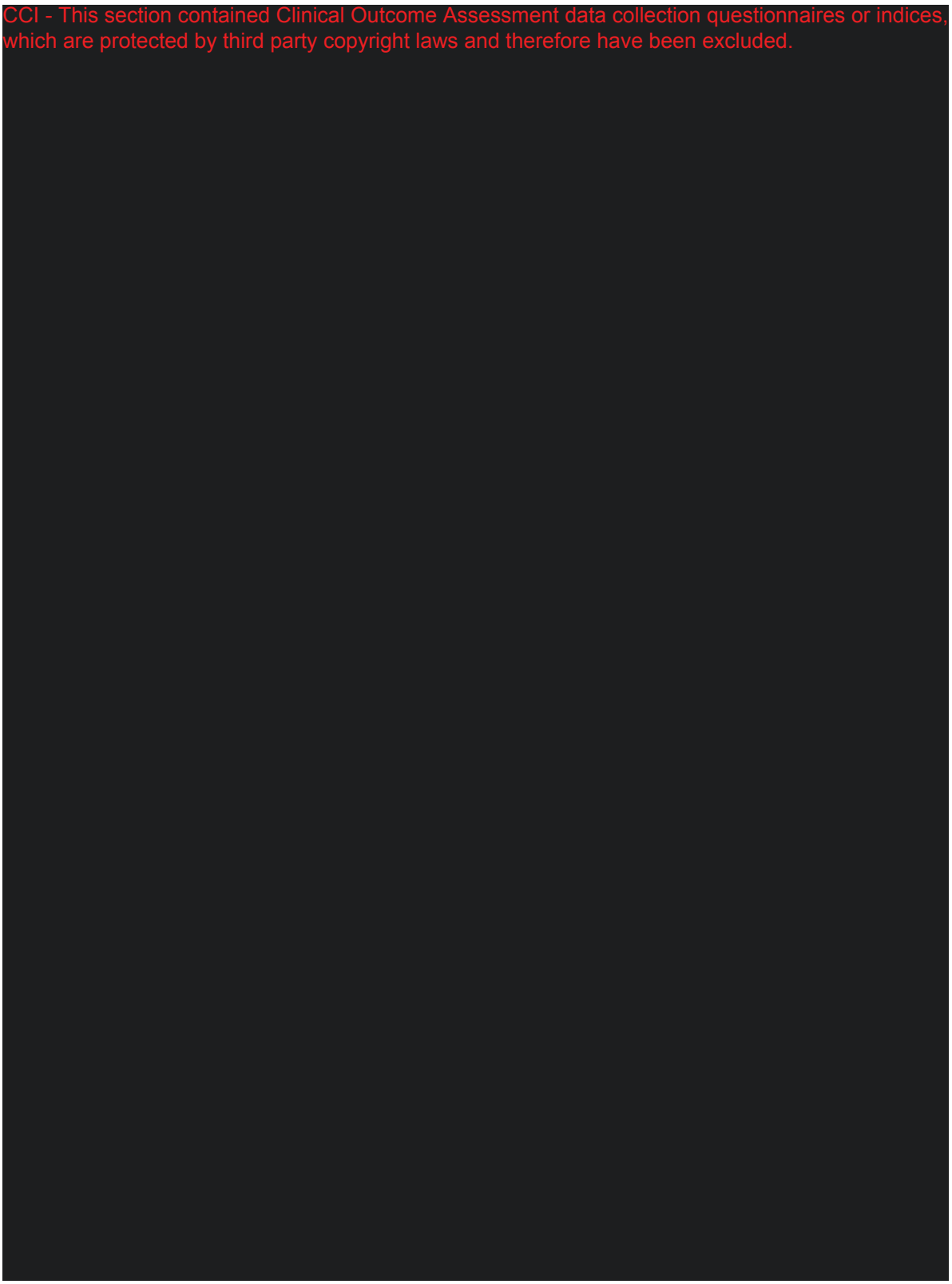
Sensory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Systemic

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Urinary

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Site Reactions to Injections and Infusions

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Laboratory Values*

Chemistries

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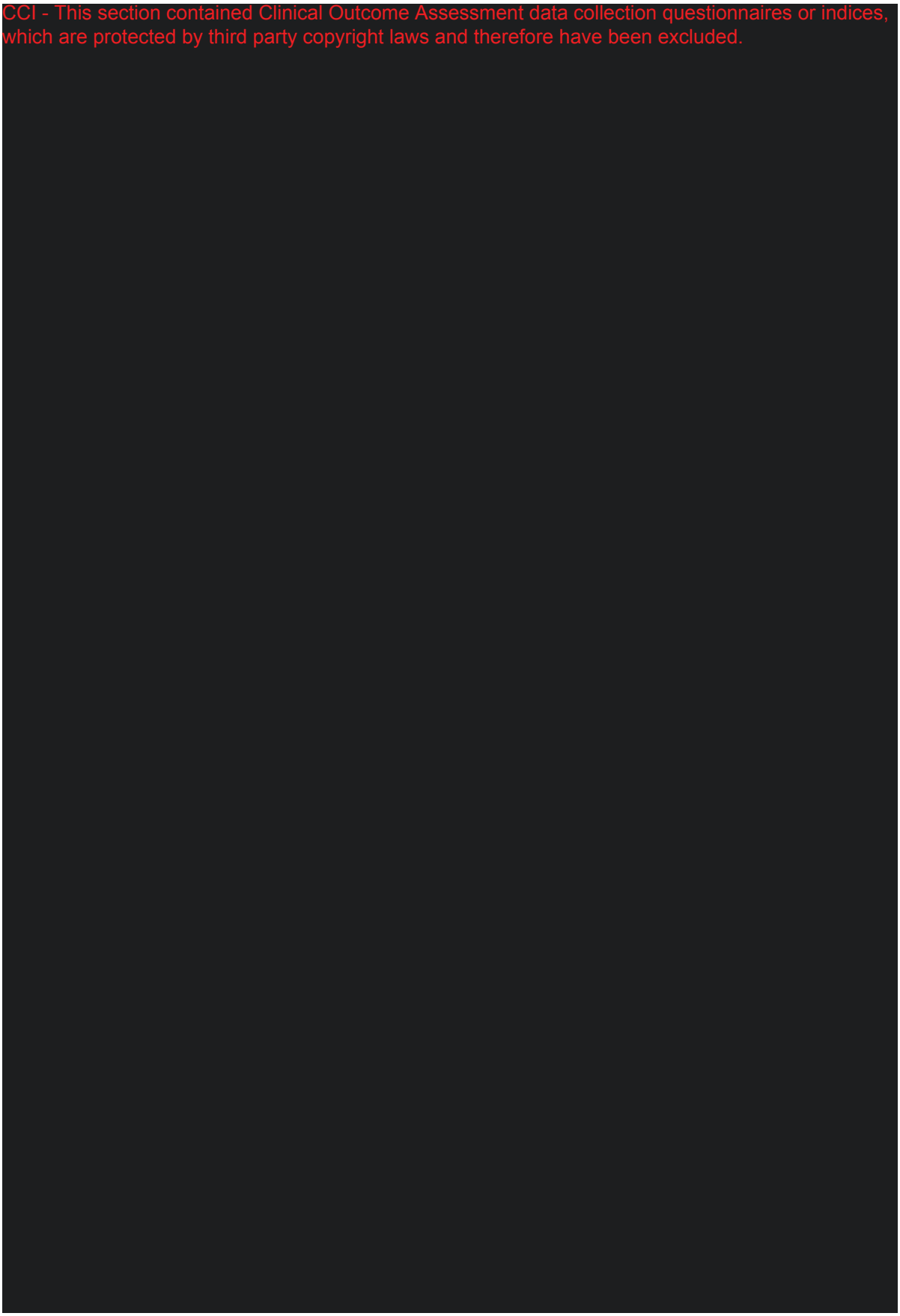
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CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

Hematology

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Urinalysis

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Appendix A: Total Bilirubin Table for Term and Preterm Neonates

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

12.8.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study 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 (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, 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.

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 (eg, 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.

12.8.2. Definition of Serious Adverse Event

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, 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.
g. Is associated with liver injury and impaired liver function defined as: ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or** ALT ≥ 3xULN and INR** > 1.5. * Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE. ** INR testing not required per protocol and the threshold value does not apply to participants receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

12.8.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

12.8.4. Sentinel Events

Sentinel Event Definition:
A sentinel event is a GSK/VHC-defined SAE that is not necessarily drug-related but has been associated historically with adverse reactions for other drugs and is therefore worthy of heightened pharmacovigilance. Medical Monitor review of all SAEs for possible sentinel events is mandated at GSK/VHC. The Medical Monitor may request additional clinical information on an urgent basis if a possible sentinel event is identified on SAE review. The current GSK/VHC-defined sentinel events are listed below: • Acquired Long QT Syndrome • Agranulocytosis/Severe neutropenia • Anaphylaxis and anaphylactoid reactions • Hepatotoxicity • Acute renal failure • Seizure • Stevens Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN)

12.8.5. Recording and Assessing AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the CRF. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to ViiV Healthcare/GSK in lieu of completion of the ViiV Healthcare/GSK /AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by ViiV Healthcare/GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to ViiV Healthcare/GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

Every AE and SAE reported during the trial should be evaluated by the investigator and graded in the eCRF according to the DAIDS toxicity scales (see Appendix 7).

Note: Grade 4 DAIDS toxicity grades for laboratory parameters that are asymptomatic would not necessarily be considered SAEs, a clinical correlation would be necessary.

Where a DAIDS toxicity scale is not available for a particular event or parameter, then the investigator will instead make an assessment of intensity using one of the following categories:

1. Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

2. Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study 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/GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to ViiV Healthcare/GSK.**

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by ViiV Healthcare/GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide ViiV Healthcare/GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to ViiV Healthcare/GSK within 24 hours of receipt of the information.

12.8.6. Reporting of SAE to ViiV Healthcare/GSK/PPD

SAE Reporting to ViiV Healthcare/GSK/PPD via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to ViiV Healthcare/GSK/PPD 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 on the Sponsor/Medical Monitor Contact Information Page of this protocol.
SAE Reporting to ViiV Healthcare/GSK/PPD 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 on the Sponsor/Medical Monitor Contact Information Page of this protocol.

	Initial Reports		**Follow-up Information on a Previous Report**	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	"SAE" data collection tool	24 hours	Updated "SAE" data collection tool
Cardiovascular or death event	Initial and follow-up reports to be completed when the cardiovascular event or death is reported	"CV events" and/or "death" data collection tool(s) if applicable	Initial and follow-up reports to be completed when the cardiovascular event or death is reported	Updated "CV events" and/or "death" data collection tool(s) if applicable
Pregnancy	24 hours	"Pregnancy Notification Form"	24 hours	"Pregnancy Follow-up Form"
ALT ≥3×ULN **and** bilirubin ≥2×ULN (>35% direct)	24 hours[a]	"SAE" data collection tool. "Liver Event eCRF" and "Liver Imaging" and/or "Liver Biopsy" eCRFs, if applicable[b]	24 hours	Updated "SAE" data collection tool/"Liver Event" documents[b]

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
ALT≥5×ULN that persists ≥2 weeks	24 hours[a]	Liver Event eCRF[b]	24 hours	Updated Liver Event eCRF[b]
ALT ≥8×ULN	24 hours[a]	Liver Event eCRF[b]	24 hours	Updated Liver Event eCRF[b]
ALT ≥3×ULN (if baseline ALT is <ULN) or ALT ≥3 fold increase from baseline value (if baseline ALT >ULN) with appearance or worsening of symptoms of hepatitis or hypersensitivity	24 hours[a]	Liver Event eCRF[b]	24 hours	Updated Liver Event eCRF[b]

a. The Medical Monitor must be contacted at onset of liver chemistry elevations to discuss participant safety.
b. Liver event documents (i.e., "Liver Event eCRF" and updates, "Liver Imaging eCRF" and/or "Liver Biopsy eCRF", as applicable) should be completed as soon as possible.

12.8.7. Reporting COVID-19 AEs and SAEs

Refer to Section 12.12.2.2 (Appendix 12 COVID-19 Guidance) for guidance on the reporting of COVID-19 specific AEs and SAEs.

12.9. Appendix 9: 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 7). Additional information regarding detecting, documenting and reporting AEs and SAEs are available in Section 9.3.1.

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 minimise 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.

[For general guidelines on the management of specific toxicities [including liver chemistry stopping and follow up criteria, restarting study drug, decline in renal function, allergic reaction, rash, hypertriglyceridaemia/hypercholesterolaemia and CPK elevation] that are considered to be related or possibly related to study treatment see Section 12.9.1 Specific Toxicities/Adverse Event Management.

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 lipid abnormalities in Section 12.9.1.6 and rash in Section 12.9.1.5

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. Exceptions are noted for lipid abnormalities in Section 12.9.1.6. 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.

12.9.1. Specific Toxicities/Adverse Event Management

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

Participants who permanently discontinue study 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 as noted in Section 12.9.

12.9.1.1. Liver Chemistry Stopping and Follow-up Criteria

Liver chemistry threshold stopping criteria have been designed to assure participant safety and to evaluate liver event aetiology during administration of study drug and the

follow-up period. For a complete listing of stopping and follow-up criteria refer to Section 8.1.2.

12.9.1.2. Restarting Study Drug

Refer to Section 8.1.4 and Section 12.5 Appendix 5 for details on drug restart following transient resolving liver events not related to study treatment.

12.9.1.3. Decline in Renal Function

Note: DTG can inhibit the tubular secretion of creatinine and can therefore be associated with a slight increase in serum creatinine and apparent decrease in the estimated glomerular filtration rate (generally by 10% or less). This typically occurs within the first 4 weeks of treatment with DTG and remains stable thereafter and is not associated with renal damage or true decline in renal function. See below for advice on management of renal toxicity by DAIDS grading.

Note: Utilize absolute creatinine or creatinine clearance value when determining the respective DAIDS severity bands.

Serum creatinine and eGFR rates will be routinely monitored in this study. At each time point when serum creatinine testing is performed, the eGFR rate will be calculated using the bedside Schwartz formula:

eGFR (mL/min/1.73 m^2) = 0.413 * height (in cm) ÷ serum creatinine (in mg/dL)

Both the serum creatinine level and the eGFR rate will be graded for severity and assessed for change from baseline and clinical significance. When abnormal results are obtained, confounding factors and other non-study drug explanations (e.g., concomitant medications, concomitant illness, dehydration) should be considered and a nephrology consult may be obtained.

Creatinine

Participants who experience an increase to Grade 2 from a normal or Grade 1 serum creatinine level at baseline, or an increase to Grade 3 from a normal, Grade 1 or Grade 2 creatinine level at baseline may continue study treatment but should undergo confirmatory testing within 2-4 weeks. Participants who develop a Grade 4 creatinine level should have study treatment temporarily held and have confirmatory testing within 2 weeks. Serum creatinine testing should be repeated and consideration should also be given to performing a urinalysis assessing urine albumin:creatinine and urine protein:creatinine ratios and if the elevation is confirmed, the study Medical Monitor should be consulted regarding further follow-up and management.

For a confirmed Grade 4 creatinine, study drug should be permanently discontinued.

eGFR

Participants who experience an increase from a normal, Grade 1, or Grade 2 eGFR at baseline to Grade 3 eGFR rate may continue study treatment but should undergo confirmatory testing within 2-4 weeks. Participants who develop a Grade 4 eGFR should have study treatment temporarily held and have confirmatory testing within 2 weeks. Other signs of renal toxicity should be sought and any alternative cause of renal impairment should be explored and treated appropriately. Consideration should also be given to assessing cystatin-C and performing a urinalysis assessing urine albumin:creatinine and urine protein:creatinine ratios.

If the increase to Grade 3 eGFR and/or a Grade 3 creatinine is confirmed, study drug should be temporarily held and the study Medical Monitor should be consulted regarding further follow-up and management.

Consideration should be given to a nephrology consultation, and the case discussed by the study team to determine benefit risk balance of continuing with study drug.

For a confirmed Grade 4 eGFR, study drug should be permanently discontinued.

Participants requiring permanent discontinuation of study drug should be followed weekly until resolution and have withdrawal study evaluations completed. A follow-up visit should be performed 4 weeks after the last dose of study drugs.

12.9.1.4. Allergic reaction

Participants may continue study drug for Grade 1 or 2 allergic reactions at the discretion of the Investigator. The participant should be advised to contact the Investigator immediately if there is any worsening of symptoms or if further systemic signs or symptoms develop. Antihistamines, topical corticosteroids, or antipruritic agents may be prescribed.

Participants with Grade ≥3 allergic reactions that are considered to be possibly or probably related to the study drug should permanently discontinue study treatment and the participant should be withdrawn from the study. Participants should be treated as clinically appropriate and followed until resolution of the AE.

12.9.1.5. Rash

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. No instances of serious skin reaction, including SJS, TEN and erythema multiforme, have been reported for DTG in clinical trials. For further characterisation of HSR and rash observed with DTG-containing ART, please see the current version of the IB [GlaxoSmithKline Document Number RM2007/00683/12].

Participants with an isolated Grade 1 rash may continue study drug at the Investigator's discretion. The participant should be advised to contact the Investigator immediately if

there is any worsening of the rash, if any systemic signs or symptoms appear, or if mucosal involvement develops.

Participants may continue study drug for an isolated Grade 2 rash. However, study drug (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. 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 study drug [and all other concurrent medication(s) suspected in the Investigators causality assessment] for an isolated Grade 3 or 4 rash, except where the aetiology of the rash has been definitively diagnosed as NOT attributable to study drug (see below), and the participant should be withdrawn from the study. Participants should be treated as clinically appropriate and followed until resolution of the AE. Every effort should be made to collect as much information as possible about the evolution of the event and any relationship with potentially related medical events (e.g. viral infection) or start of concomitant medication.

The rash and any associated symptoms should be reported as adverse events and appropriate toxicity ratings should be used to grade the events (based on DAIDS toxicity gradings, Section 12.7).

However, if the aetiology of the rash has been definitively diagnosed as being unrelated to study drug and due to a specific medical event or a concomitant infection or a concomitant non-study medication, routine management should be performed and documentation of the diagnosis provided. In this situation, the study drug should be continued.

12.9.1.6. Hypertriglyceridemia/Hypercholesterolemia

Samples for lipid measurements must be obtained in a fasted state according to the Schedule of Activities Table (Section 2). Participants who experience asymptomatic triglyceride or cholesterol elevations may continue to receive study drug.

12.9.1.7. Creatine Phosphokinase (CPK) 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.

12.10. Appendix 10: Modified List of Highly Effective Methods for Avoiding Pregnancy and Collection of Pregnancy Information

12.10.1. Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

The list does not apply to FRP with same sex partners or for participants who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

FRP are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described

1. Contraceptive subdermal implant
2. Intrauterine device or intrauterine system
3. Combined estrogen and progestogen oral contraceptive [Hatcher, 2011]
4. Injectable progestogen [Hatcher, 2011]
5. Contraceptive vaginal ring [Hatcher, 2011]
6. Percutaneous contraceptive patches [Hatcher, 2011]
7. Male partner sterilisation with documentation of azoospermia prior to the female participant's entry into the study, and this male is the sole partner for that participant [Hatcher, 2011].The documentation on male sterility can come from the site personnel's review of participant's medical records, medical examination, and/or semen analysis, or medical history interview provided by her or her partner.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that participants understand how to properly use these methods of contraception.

12.10.2. Collection of Pregnancy Information

- 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/GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to ViiV Healthcare/GSK/PPD Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. GSK's central safety department also will forward this information to the Antiretroviral Pregnancy Registry. The international registry is jointly sponsored by manufacturers

or licensees of antiretroviral products. Additional information and a list of participating manufacturers/licensees are available from http://www.apregistry.com/.

- 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/GSK as described in Section 12.8.6. 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.

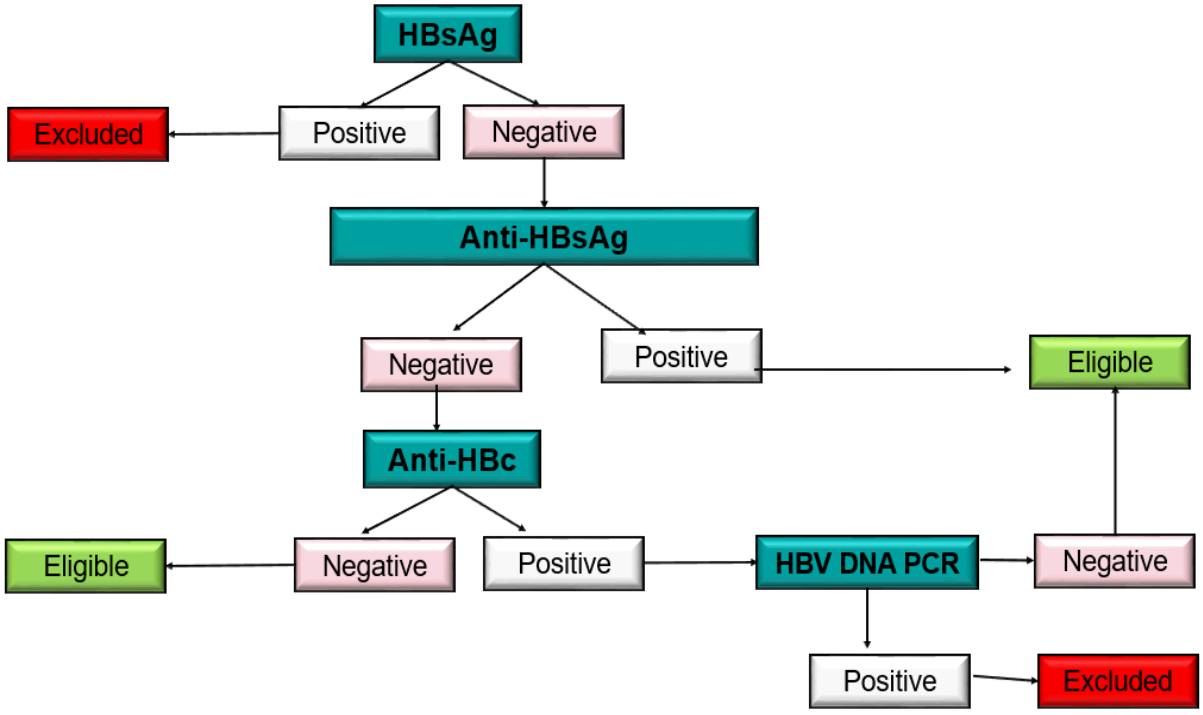
Any female participant who becomes pregnant (intrauterine) while participating in this study must be withdrawn from the study and must immediately discontinue study drug.

Reference

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, editors. Contraceptive Technology. 19th edition. New York: Ardent Media, 2007:28.

Hatcher RA, Trussell J, Nelson AL, et al, editors. Contraceptive Technology. 20th edition. Atlanta, Georgia: Ardent Media, Inc., 2011: 50. Table 3-2.

12.11. Appendix 11: Decision Flow- Screening Tests for Hepatitis B Virus Serology, Interpretation and Action



12.12. Appendix 12: COVID-19 Guidance

12.12.1. COVID -19 Experimental Agents

If any treatments for COVID-19 are planned for a study participant, please consult with the study medical monitor to ensure that relevant drug interactions are considered and to ensure that continued study participation remains appropriate.

12.12.2. COVID-19 Specific Data Capture

12.12.2.1. Capturing COVID-19 Specific Protocol Deviations

Your PPD Monitor will provide specific guidance on capturing protocol deviations as a result of COVID-19, if needed.

12.12.2.2. Capturing COVID-19 Specific AEs and SAEs

It is important for the study team to describe COVID-19 related adverse events/serious adverse events and their impact on study data and outcomes. Standardization of case definitions will facilitate future data analysis.

Please use the following guidance:

1. AEs should continue to be evaluated as to whether they meet SAE criteria as defined in the protocol, and if so, submitted according to established SAE reporting requirements. SAEs and AEs should be submitted following usual study procedures and timelines.

2. When an in-person clinic visit is not possible, please conduct a remote telehealth visit to assess for, and document any AEs/SAEs.

3. Investigators should use the WHO definition to classify COVID-19 cases. The definition below, released 20 March 2020, represents a time point for standardized collection. We recognize definitions are likely to continue to evolve. When reporting both serious and non- serious adverse events (related to COVID-19 infection, investigators should use the following Verbatim terms:
    a. Suspected COVID-19 infection; or
    b. Probable COVID-19 infection; or
    c. Confirmed COVID-19 infection.

4. Sites should contact the study Medical Monitor for questions related to definitions and reporting, and decisions around impact to study drug continuation.

5. A new COVID-19 infection Case Report Form has been added to the eCRF to collect additional details about the reported COVID-19 AE or SAE data. It is important to collect the correct information from each participant reporting a COVID-19 AE or SAE. Therefore, please use the CRF templates to collect this information.

WHO Case Definition – 20 March 2020 Version (https://www.who.int/publications-detail/global-surveillance-for-human-infection-with-novel-coronavirus-(2019-ncov))**:**

Suspected case:

A. A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath), AND a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset;

OR

B. A patient with any acute respiratory illness AND in contact (see definition of "contact" below) with a confirmed or probable COVID-19 case (see definition of contact) in the last 14 days prior to symptom onset;

OR

C. A patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath; AND requiring hospitalization) AND in the absence of an alternative diagnosis that fully explains the clinical presentation.

Probable case:

A. A suspect case for whom testing for the COVID-19 virus is inconclusive (Inconclusive being the result of the test reported by the laboratory).

OR

B. A suspect case for whom testing could not be performed for any reason.

Confirmed case:

A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.

Covid-19 Contact:

A contact is a person who experienced any one of the following exposures during the 2 days before and the 14 days after the onset of symptoms of a probable or confirmed case:

1. Face-to-face contact with a probable or confirmed case within 1 meter and for more than 15 minutes;
2. Direct physical contact with a probable or confirmed case;
3. Direct care for a patient with probable or confirmed COVID-19 disease without using proper personal protective equipment; OR

4. Other situations as indicated by local risk assessments.

Note: for confirmed asymptomatic cases, the period of contact is measured as the 2 days before, through the 14 days after the date on which the sample was taken which led to confirmation.

12.13. Appendix 13: Protocol Amendment History

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

Amendment 1, 13-Jun-2018

Overall Rationale for the Amendment:

In one ongoing birth outcome surveillance study in Botswana, early results from an unplanned interim analysis show that 4/426 (0.9%) of women who were taking DTG when they became pregnant had babies with neural tube defects compared to a background rate of 0.1%.

Risk of neural tube defect was added to the Benefit/Risk Assessment for this study.

The protocol was updated to reinforce the importance of pregnancy avoidance and contraception requirements.

A correction to the timing of intensive PK sample collection was made within the Schedule of Activities footnote.

Section # and Name	Description of Change	Brief Rationale
Section 2, Schedule of Activities: Sample for pharmacokinetic analysis (intensive serial collection-subset of participants	Footnote corrected to remove sample collection timepoints at 8 and 12 hours and insert a sample collection timepoint at 10 hours.	Clarification of collection timepoints for intensive PK sampling.
Section 2, Schedule of Activities: Pregnancy Testing	Footnote added for Investigators and/or site staff to remind females of reproductive potential of the need to avoid pregnancy while in study and adhere to the study's contraception requirements.	Updated to reinforce the importance of pregnancy avoidance and contraception requirements.
Section 3.3.1, Risk Assessment	DTG: Addition of neural tube defects as a potential risk of clinical significance during use in pregnancy. Updated mitigation strategy.	In one ongoing birth outcome surveillance study in Botswana, early results from an unplanned interim analysis show that 4/426 (0.9%) of women who were taking DTG when they became pregnant had babies with neural tube defects compared to a background rate of 0.1%. Risk of neural tube defect was added to the Benefit/Risk Assessment for this study.
Section 6.1, Inclusion Criteria	Change in the timeframe for use of acceptable methods of birth control by females of reproductive potential (FRP) to require use 28 days prior to the first dose of study medication until the last dose of study medication and completion of the Follow-up visit (4 weeks after the last dose). Original timeframe required use prior to the first dose of study medication and up to 2 weeks after the last dose of study medication.	Refined to allow time for start of hormonal methods of birth control and reduce the likelihood of pregnancy in females of reproductive potential during exposure to dolutegravir.

Section # and Name	Description of Change	Brief Rationale
Section 8.2, Withdrawal form Study and Stopping Criteria	Addition of a reminder noting females of reproductive potential who change their minds and desire to be pregnant, or who state they no longer are willing to comply with the approved pregnancy methods, should also be withdrawn from the study.	Updated to reinforce the importance of pregnancy avoidance and contraception requirements.
Section 11, References	DTG Investigator's Brochure version 11, supplements 01 and 02 were added to reference list.	DTG Investigator's Brochure (IB) version update.
Section 12.10.1, Appendix 10, Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)	Removal of male condom combined with vaginal spermicide (foam, gel, film, cream, or suppository) from the list of highly effective methods for avoiding pregnancy.	List of acceptable highly effective methods of contraception was refined to reduce the likelihood of pregnancy in females of reproductive potential during exposure to dolutegravir.

Amendment 2, 13-Nov-2019

Overall Rationale for the Amendment:

A Continuation Phase is incorporated to enable post study drug provision for eligible participants who may benefit from continued treatment. If required by local regulations, study participants who have successfully completed both the Treatment Phase through Week 48 and the Extension Phase through Week 144 will be given the opportunity to continue to receive DTG/3TC once daily in the Continuation Phase, regardless of age, until: DTG and 3TC are both locally approved for use as part of a dual regimen, and the single entities of DTG and 3TC are available to patients (e.g. through public health services), or the DTG/3TC FDC tablet is locally approved and available (e.g. commercially or through public health services), or the participant no longer derives clinical benefit or meets a protocol-defined reason for discontinuation. Analyses may be conducted as necessary after Week 144 to support regulatory submissions and publications.

A planned 96-week secondary analysis is incorporated to assess long-term durability of response and evaluate potential risk of resistance associated substitutions.

A change in weight entry criterion, from 40 kg and above to 25 kg and above, is incorporated. This change is supported by current dosing recommendations for 3TC in pediatric patients weighing 25 kg and above (300 mg daily, taken as 150 mg BID or 300 mg QD, as per EPIVIR product label) and recent pharmacokinetic data from the ODYSSEY study which supports use of DTG at the adult dose (50 mg) in children weighing 25 kg and above.

Section # and Name	Description of Change	Brief Rationale
Protocol Title Section 1 Summary	• Addition of compound number for fixed dose combination DTG/3TC • Change in adolescent weight cut off from 40 kg to 25 kg.	• Compound numbers for single entities (DTG and 3TC) were included within the original Protocol Title page. Compound number for the DTG/3TC Fixed Dose Combination (FDC) used in this study was added for clarity. • Current dosing recommendations for 3TC in paediatric patients weighing ≥25 kg is 300 mg daily and can be taken as 150 mg BID or 300 mg QD [EPIVIR PI]; Recent pharmacokinetic data from the ODYSSEY study supports use of DTG

Section # and Name	Description of Change	Brief Rationale
		at the adult dose (50 mg) in children weighing ≥25 kg.
Medical Monitor/SAE Contact information	• Shifted PPD Medical Monitor and SAE reporting information from footnote to body of table.	• PPD Medical Monitor and Safety Hotline are first line points of contact for sites. Information embedded within table to facilitate reference.
Section 2 Schedule of Activities	• Added Continuation Phase and applicable Continuation Phase assessments after the Week 144 Visit. • Added collection of fasting lipids, glucose and HbA1c at the time of withdrawal from the study if the withdrawal visit occurred at weeks 48, 96 or 144. • Added note stating CSSRS participant level reports should be reviewed, signed by Investigator or Sub-Investigator and files in site source with actions taken for positive findings clearly documented. • Table was reformatted for clarity. Footnotes were incorporated within each applicable assessment line item. Assessment timepoint markings ('X') were reformatted to reflect actual assessment timepoint (such as SC for screening visit, B for baseline visit, etc.).	• A Continuation Phase was added to enable post study drug provision for eligible participants who may benefit from continued treatment. • Serum lipid and blood glucose levels may increase during antiretroviral therapy. Collection of fasting lipids, glucose and HbA1c at the time of withdrawal from the study at weeks 48, 96 or 144 was added to align with data collection in the adult DOVATO studies (GEMINI-1 and GEMINI-2). • Investigator review of CSSRS reports, and documentation of the review and any action taken, is important. A reminder regarding required documentation at the site was added to the table. • Schedule of Activities table was reformatted to facilitate reference.
Section 3 Introduction	• Added 48-week and 96-week results from GEMINI-1 and GEMINI-2 studies. • Referenced DOVATO approval	• GEMINI-1 and GEMINI-2 48-week and 96-week study results were incorporated for completeness. • Reference to recent DOVATO approvals added for completeness.

Section # and Name	Description of Change	Brief Rationale
Section 3.1 Background	• Added 48-week and 96-week results from GEMINI-1 and GEMINI-2 studies.	• GEMINI-1 and GEMINI-2 48-week and 96-week study results were incorporated for completeness.
Section 3.3 Benefit:Risk Assessment	• Added DOVATO product label as reference.	• Reference added for completeness.
Section 3.3.1 Benefit:Risk Assessment- Neural Tube Defect	• Updated risk of neural tube defect to reflect current data (change in rate from 0.9% to 0.3%). The following update was provided: In a birth outcome surveillance study in Botswana there have been 5 cases of neural tube defects reported in 1,683 deliveries (0.3%) to mothers taking dolutegravir-containing regimens from the time of conception, compared with 15 cases in 14,792 deliveries (0.1%) to mothers taking non-dolutegravir-containing regimens from the time of conception. In the same study, one out of 3,840 deliveries (0.03%) to mothers who started dolutegravir during pregnancy had a neural tube defect, compared with three out of 5,952 deliveries (0.05%) to mothers who started non-dolutegravir-containing regimens during pregnancy.	• Recent data from surveillance study in Botswana added for completeness.
Section 3.3.1 Risk Assessment Section 7.9.2 Prohibited Medications and Non-Drug Therapies	• Addition of fampridine (also known as dalfampridine) to the list of prohibited medications.	• Fampridine (also known as dalfampridine), is a substrate of organic cation transporter 2 (OCT2) with a narrow therapeutic window, similar to dofetilide, that should not be administered concurrently with the DTG containing

Section # and Name	Description of Change	Brief Rationale
		products due to the potential risk of seizures.
Section 5 Study Design Section 5.3 Participant and Study Completion	• Noted that a participant will be considered to have completed the Continuation Phase after completion of the End of Continuation Phase Visit. • Updated Study Schematic to include Continuation Phase and planned 96-week secondary analysis.	• An End of Continuation Phase Visit will be completed for participants transitioning to approved and locally available supply. • A planned 96-week secondary analysis was incorporated to assess long-term durability of response and evaluate potential risk of resistance associated substitutions.
Section 5.5 Dose Justification	• Added reference to DOVATO approvals • Added rationale for modification of weight entry criterion (change from 40 kg to 25 kg)	• Reference to recent DOVATO approvals added for completeness. • Current dosing recommendations for 3TC in paediatric patients weighing ≥25 kg is 300 mg daily and can be taken as 150 mg BID or 300 mg QD [EPIVIR PI]; Recent pharmacokinetic data from the ODYSSEY study supports use of DTG at the adult dose (50 mg) in children weighing ≥25 kg.
Section 6.1 Inclusion Criteria	• Inclusion #2 Change in weight entry criterion from ≥40 kg to ≥25 kg. • Inclusion #4- Added inclusion of PEP/PrEP dose >6 months from HIV diagnosis or there is documented HIV seronegativity at least 2 months after the last prophylactic dose and prior to the date of HIV diagnosis.	• Inclusion #2: Current dosing recommendations for 3TC in paediatric patients weighing ≥25 kg is 300 mg daily and can be taken as 150 mg BID or 300 mg QD [EPIVIR PI]; Recent pharmacokinetic data from the ODYSSEY study supports use of DTG at the adult dose (50 mg) in children weighing ≥25 kg. • Inclusion #4- PEP/PrEP guidance added for completeness.

Section # and Name	Description of Change	Brief Rationale
Section 6.2 Exclusion Criteria	• Exclusion #7- Untreated syphilis infection (positive rapid plasma reagin [RPR] at Screening without clear documentation of treatment) is exclusionary. The original criterion required participants completed syphilis treatment at least 14 days prior to screening. The timeframe required for completion of syphilis treatment prior to screening was modified from 'at least 14 days' to 'at least 24 hours'. • Exclusion #2- Removed WHO Stage 3 exclusion as follows: Any evidence of an active Centers for Disease Control and Prevention (CDC) Stage3 and/or Category C or WHO Stage ~~3 or~~ 4 disease (Appendix 6, Section 12.6), except cutaneous Kaposi's sarcoma not requiring systemic therapy and historical or current CD4 cell counts less than 200 cells/mm3 or CD4% <15%. • Exclusion #21- Addition – exclusion of children who are wards of the state or government.	• Exclusion #7: Patients with active syphilis, untreated or partially treated, may have or develop adverse events as part of their syphilitic disease, which may be confused with a potential IP effect. Thus, completion of syphilis treatment prior to initiation of IP is preferred. Adverse reactions to syphilis treatment, such as Jarisch-Herxheimer reaction, typically occur within 24 hours after completion of treatment [Butler, 2017; Yang, 2010]. The required timeframe for completion of syphilis treatment prior to Day 1 of the study was reduced to at least 24 hours. This change accounts for the timeframe in which adverse reactions may occur, while mitigating risk for delay in assessing eligibility and patient access to study treatment. • Exclusion #2: WHO Stage 3 was removed as exclusion as it is largely equivalent to CDC Stage 2, which is not exclusionary, and WHO Stage 4 is most similar to CDC Stage 3. • Exclusion #21: As per ViiV Healthcare policy, Children who are wards of state (children in care) should not be enrolled in this study.
Section 7.10 Treatment after the End of Study	• Addition of Continuation Phase. • Addition of End of Continuation Phase Visit	• A Continuation Phase was added to enable post study drug provision for eligible

Section # and Name	Description of Change	Brief Rationale
		participants who may benefit from continued treatment. • The purpose of the End of Continuation Phase Visit is to document participant transition to locally approved and available DTG+3TC.
Section 9.6 Pharmacokinetic	• Added sub section 9.6.1.2 Collection of Ctrough samples- All Participants	• Added sub heading for collection of Ctrough samples for clarity
Section 9.6.1.1 Collection of Sparse PK samples – All Participants	• Added footnote reminder - participants are to complete a dosing diary card for 3 days prior to PK sampling Visits.	• Completed Dosing Diary Cards will be collected for Ctrough, sparse and intensive PK visits.
Section 9.6.2 Important Information on collection of PK samples	• Added Sub section 9.6.2.1. for Timing of Sparse PK Samples and Dosing Diary Cards • Added Sub section 9.6.2.2. and clarification noting dosing diary cards should be collected 3 days prior to scheduled Ctrough, sparse or intensive PK clinic visits.	• Sub heading was added to facilitate reference within the Table of Contents. • Completed Dosing Diary Cards will be collected for Ctrough, sparse and intensive PK visits.
Section 10.3.1 Efficacy Analyses	• Added details that analyses for Weeks 96 and 144 will be provided in RAP	• For better clarity
Section 10.3.5 Secondary Analyses	• A planned Week 96 secondary analysis is added. At least 3 analyses will be conducted to evaluate the primary and secondary objectives (at Weeks 48,96 and 144). Further data cuts and analyses may be conducted as necessary after Week 144 to support regulatory submissions and publications. • Timing and triggers for Independent data monitoring committee (IDMC) data looks and meetings were added.	• A planned Week 96 secondary analysis was incorporated to assess long-term durability of response and evaluate potential risk of resistance associated substitutions • Clarification incorporated to note three planned analyses timepoints and potential for further data cuts and analyses as necessary to support regulatory submissions and publications.

Section # and Name	Description of Change	Brief Rationale
		• Timings and triggers for IDMC data looks and meetings were added for completeness and transparency.
Section 11 References	• References updated	• Updated references to align with amendment modifications for completeness.
Section 12.1 (Appendix 1) Abbreviations and Trademark Information	• DOVATO added to ViiV Healthcare group of companies list of trademarks.	• Updated with DOVATO trademark for completeness.
Section 12.11 (Appendix 11) Decision Flow-Screening Tests for Hepatitis B Virus Serology, Interpretation and Action	• A decision flow chart, to assist in the interpretation of hepatitis B virus serology results, is added for reference.	• Added for reference and clarity.
Throughout	• Corrected inconsistencies, links and typos, and updated abbreviations	• To improve quality of the protocol