TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A Phase III, randomised, double-blind, multicentre, parallel-group, non-inferiority study evaluating the efficacy, safety, and tolerability of dolutegravir plus lamivudine compared to dolutegravir plus tenofovir/emtricitabine in HIV-1-infected treatment-naïve adults

Compound Number: GSK1349572 + GR109714 (GSK3515864)

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Author (s): PPD

Revision Chronology

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2015N242978_00	2016-APR-25	Original
2015N242978_01	2017-DEC-01	Amendment No. 1

The double barrier method of contraception (male condom combined with a vaginal spermicide) was added in this study as a permitted method for preventing pregnancy in females of reproductive potential.

Exclusion criterion #15 (limitations on investigational drug use) was broadened to include additional countries as needed. Inclusion of Portugal was required by the Portuguese National Ethics Committee for Clinical Research.

Assessment of weight at Weeks 96 and 144 was added to monitor the incidence of significant weight gain with dolutegravir use.

Assessment of inflammation biomarkers (IL-6, hs-CRP) at Day 1, and Weeks 48, 96 and 144, was added as a new exploratory endpoint.

Assessment of telomere length at Day 1, and Weeks 96 and 144, was added as a new exploratory endpoint.

For clarification purposes, the 'peripheral blood mononuclear cell (PBMC)' sample in Section 7.1 (Time and Events table) and Section 7.6.1 (HIV-1 Exploratory Analyses) was renamed as a 'whole blood' sample.

The Day 1 'PBMC' sample (now named 'whole blood' sample) originally designated for virology use was additionally designated for telomere length measurement, where possible. Additional whole blood samples were added for measurement of telomere length at Week 96 and Week 144.

A description of commercial image dolutegravir tablets was added to Section 6.1 (Investigational Product and Other Study Treatment) to allow use of commercial material as well as clinical trial material during the study.

The physical description for open-label lamivudine in Section 6.1 was corrected.

Standard procedures for forwarding pregnancy information to the Antiretroviral Pregnancy Register were added.

For clarification purposes, the AE severity gradings in Appendix 7, Section 12.7.6 (Evaluating AEs and SAEs) were updated to be consistent with Appendix 6, Section 12.6. (Division of AIDS table for Grading Severity of Adult and Pediatric Adverse Events). This change has no impact on the investigator's evaluation of adverse events.

Minor revisions were made to the text to provide updated information, correct errors and improve accuracy and consistency.

SPONSOR SIGNATORY

PPD

December 1, 2017

Kimberly Y. Smith, MD, PPD
Vice President and Head,
Global Research and Me gy,
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Date

PPD

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

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

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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 VP and Head, Global Research and Medical Strategy.

Regulatory Agency Identifying Number(s): US IND 75,382; EudraCT 2015-004418-95

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 204861

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:	
Investigator Address:	
Investigator Phone Number:	

Investigator Signature	Date

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1. PROTOCOL SYNOPSIS FOR STUDY 204861

Rationale

Study 204861 is being conducted to compare a simplified two-drug regimen of dolutegravir (DTG) plus lamivudine (3TC) with a standard three-drug first-line regimen in human immunodeficiency virus type 1 (HIV-1) infected, antiretroviral therapy (ART)-naïve adult subjects. The study is designed to demonstrate the non-inferior antiviral activity of DTG plus 3TC once daily compared to DTG plus tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) fixed-dose combination (FDC) once daily at 48 weeks. This study will also characterise the long-term antiviral activity, tolerability and safety of DTG plus 3TC through Week 148.

An identical sister study, 205543, will be conducted in parallel with Study 204861 in some countries. The clinical development programme of DTG plus 3TC aims to develop a FDC tablet of these products.

Objectives/Endpoints

Objectives	Endpoints
Primary	
• To demonstrate non-inferior antiviral activity of DTG + 3TC versus DTG + TDF/FTC at 48 weeks in HIV-1-infected, ART-naïve subjects	• Proportion of subjects with plasma HIV-1 RNA <50 copies/mL (c/mL) at Week 48 using the FDA Snapshot algorithm [Missing, Switch or Discontinuation = Failure (MSD=F)] for the intent-to-treat exposed (ITT-E) population
Secondary	
• To demonstrate the antiviral activity of DTG + 3TC versus DTG + TDF/FTC at 24, 96 and 144 weeks	• Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Weeks 24, 96 and 144 using the FDA Snapshot algorithm (MSD=F) for the ITT-E population
• To evaluate the antiviral activity, immunological effects, and incidence of disease progression (HIV-associated conditions, AIDS and death) of DTG + 3TC compared to DTG + TDF/FTC over time	• Time to viral suppression (HIV-1 RNA <50 c/mL); • Absolute values and changes from Baseline in CD4+ cell counts at Weeks 24, 48, 96 and 144; • Incidence of disease progression (HIV-associated conditions, AIDS and death).
• To assess viral resistance in subjects meeting confirmed virologic withdrawal (CVW) criteria	• Incidence of treatment-emergent genotypic and phenotypic resistance to DTG and 3TC or TDF/FTC in subjects meeting CVW criteria
• To evaluate the safety and tolerability of DTG + 3TC compared to DTG + TDF/FTC over time	• Incidence and severity of adverse events (AEs) and laboratory abnormalities; • Proportion of subjects who discontinue treatment due to AEs over 24, 48, 96 and 144 weeks

Objectives	Endpoints
• To evaluate renal biomarkers (in urine and blood) and bone biomarkers (in blood) in subjects treated with DTG + 3TC compared to DTG + TDF/FTC	• Change from Baseline in renal and bone biomarkers at Weeks 24, 48, 96 and 144
• To evaluate the effects of DTG + 3TC on fasting lipids compared to DTG + TDF/FTC over time	• Change from Baseline in fasting lipids at Weeks 24, 48, 96, and 144; • The incidence of Grade 2 or greater laboratory abnormalities in fasting LDL cholesterol by Weeks 24, 48, 96, and 144;
• To evaluate the effect of patient demographics and baseline characteristics (e.g. demographic factors, HIV-1 subtype, baseline CD4+ cell count) on response to DTG + 3TC compared to DTG + TDF/FTC over time	• Proportion of subjects by patient subgroup(s) (e.g. by age, gender, Baseline CD4+ cell count) with plasma HIV-1 RNA <50 c/mL at Weeks 24, 48, 96 and 144 using the Snapshot algorithm for the ITT-E population • Change from Baseline in CD4+ cell counts at Weeks 24, 48, 96 and 144 by patient subgroups
• To assess change in health-related quality-of-life for subjects treated with DTG plus 3TC compared to DTG + TDF/FTC	• Change from Baseline in health related quality of life using EQ-5D-5L at Weeks 4, 24, 48, 96, and 144 (or Withdrawal from the study)

Overall Design

This study is a Phase III, randomised, double-blind, active-controlled, multicentre, parallel-group, non-inferiority study. The study will enrol approximately 700 HIV-1 infected, ART-naïve subjects with a Screening HIV-1 RNA of 1000 to ≤500,000 copies/mL (c/mL). Subjects will be randomised 1:1 to receive a two-drug regimen of DTG plus 3TC once daily (approximately 350 subjects) or DTG plus the FDC tablet of TDF/FTC once daily (approximately 350 subjects) until Week 148. Subjects will be stratified by screening HIV-1 RNA (≤100,000 c/mL or >100,000 c/mL) and Screening CD4+ cell count (≤ or >200 cells/mm^3).

The study initially will enrol approximately 100 subjects with a Screening HIV-1 RNA of 1000 to ≤100,000 c/mL. Accumulated data from other clinical trials investigating the DTG plus 3TC dual regimen will undergo independent review. If the independent review is supportive of evaluating the dual regimen's efficacy in subjects with a Screening viral load of up to 500,000 c/mL, recruitment will be opened to subjects with a Screening HIV-1 RNA of 1000 to ≤500,000 c/mL. If the review does not support enrolment of such subjects, the Screening viral load will remain capped at ≤100,000 c/mL. This independent review of accumulated data on the DTG plus 3TC dual regimen was supportive, enabling an increase in the Screening viral load cap to ≤500,000 c/mL for subjects screened on/after 5 November 2016.

Treatment Arms and Duration

The study will comprise a 28-day Screening Phase (which may be extended to 35 days to allow receipt of all Screening assessment results), a Double-blind Randomised Phase (Day 1 to Week 96), and an Open-label Randomised Phase (Week 96 to Week 148). If required by local regulations, subjects randomised to receive DTG plus 3TC once daily who successfully complete 148 weeks of treatment will continue to have access to DTG plus 3TC once daily (Continuation Phase) until (i) 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 (ii) the DTG/3TC FDC tablet, if required by local regulations, is available, or (iii) the subject no longer derives clinical benefit, or (iv) the subject meets a protocol-defined reason for discontinuation, or (v) development of the DTG plus 3TC dual regimen is terminated. Subjects randomised to the DTG plus TDF/FTC FDC arm will receive DTG plus TDF/FTC FDC through their Week 148 visit only, after which subjects will complete the study and will need to have alternate arrangements in place to access antiretroviral medication. No dose reductions, modifications in dosage, or changes in the frequency of dosing will be allowed in this study.

At Weeks 28, 52, 100, and 148, a confirmatory viral load measurement will be performed for subjects presenting with HIV-1 RNA ≥50 c/mL at the Week 24, 48, 96 and 144 visits, respectively. The primary and secondary efficacy endpoints correspond to viral load measurements collected within a ≤6 week window around the visits of interest (including data from the visits at Weeks 28, 52, 100, and 148), as per the FDA's Snapshot algorithm. For this reason, the primary and secondary analyses are denoted as occurring at Weeks 24, 48, 96 and 144 with the understanding that respective data from the Week 28, 52, 100 and 148 visits may be included.

An Independent Data Monitoring Committee (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 and sister study 205543.

Type and Number of Subjects

The study will be conducted in approximately 700 HIV-1 infected, ART-naïve adults with a Screening HIV RNA of 1000 to ≤500,000 c/mL. Approximately 950 subjects will be screened such that approximately 700 subjects are enrolled into the study.

Analysis

The primary analysis at Week 48 will take place after the last subject has had their Week 48 viral load assessed, including a retest if required. The primary analysis method for the proportion of responders at Week 48 will be a Cochran-Mantel-Haenszel test stratified by Baseline plasma HIV-1 RNA (≤ vs. >100,000 c/mL) and Baseline CD4+ cell count (≤ vs. >200 cells/mm^3).

Assuming a true 87% response rate in the DTG plus 3TC arm and an 89% response rate in the DTG plus TDF/FTC FDC arm at Week 48, a non-inferiority margin of -10%, and a 2.5% one-sided significance level, this study requires 347 subjects per treatment arm. This would provide 90% power to show non-inferiority for the proportion of subjects with plasma HIV-1 RNA <50 c/mL at 48 weeks. If we observed an 89% response rate for the DTG plus TDF/FTC FDC arm, non-inferiority would be declared if the observed treatment difference was better than -4.8 percentage points.

2. INTRODUCTION

2.1. 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 [BHIVA, 2015; DHHS, 2016; EACS, 2015; IAS-USA, 2014]. While these regimens are highly efficacious and generally well tolerated, there is growing concern about long-term toxicities, and great interest from patients and clinicians in unique regimens that might avoid such toxicities, and to provide effective long-term ART with the most streamlined regimens possible.

Contemporary potent 3-drug antiretroviral treatment has led to remarkable declines in morbidity and mortality in treated HIV-infected persons. However, this longer life expectancy has been accompanied by higher rates of non-acquired immuno-deficiency syndrome (AIDS)-defining events such as cardiovascular disease, liver disease and cancer. These non-AIDS-defining events are now the leading causes of morbidity and mortality among treated HIV-infected persons. The aetiologies of these non-AIDS-defining events are multi-factorial and may include chronic inflammation and immune activation, behavioural and lifestyle related factors, co-morbidities and the adverse effects of ART. In addition, as HIV-infected persons live longer, aging-associated co-morbidities are being seen with greater frequency, and this multi-morbidity often requires concomitant use of other medications. As ART needs to be taken life long, there is an unmet need for streamlined regimens that can minimize antiretroviral-related long-term toxicities and drug-drug interactions while maintaining viral suppression. Even modest improvements in side effects will have a big impact on the tolerability of, and adherence to life-long treatment regimens.

Two-drug antiretroviral regimens may maintain virologic suppression while minimizing the adverse effects from cumulative drug exposure and preserving future antiretroviral treatment options. While contemporary regimens avoid many of the liabilities of older agents, the consequences of long-term exposure to a 2-NRTI backbone remain uncertain. Chronic exposure to NRTIs may lead to telomerase and mitochondrial dysfunction, processes that may lead to accelerated aging, lipodystrophy, steatohepatitis and other aging-related morbidities [Solomon, 2014]. NRTIs have been linked to reduced telomerase activity in peripheral blood mononuclear cells (PBMCs) from HIV-infected patients [Leeansyah, 2013]. Of a multitude of NRTIs studied in vitro, tenofovir at therapeutic concentrations was found to produce the most significant inhibition of

telomerase leading to accelerated shortening of telomere length in activated PBMCs [Leeansyah, 2013; Stella-Ascariz, 2017].

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, 2017; GlaxoSmithKline Document Number RM2007/00683/11].

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™) [EPIVIR Package Insert, 2017], it is also available as part of two backbone FDC products (zidovudine (ZDV)/3TC, COMBIVIR™ and abacavir (ABC)/3TC, EPZICOM™/KIVEXA™). 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 [GlaxoSmithKline Document Number RM2007/00683/11; Walmsley, 2013].

DTG plus 3TC may provide 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 could be 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).

Study 204861 compares a simplified two-drug regimen of DTG plus 3TC once daily with one of the preferred first line three-drug regimens consisting of DTG plus two NRTIs (TDF/FTC FDC) once daily [BHIVA, 2015; DHHS, 2016; EACS, 2015; IAS-USA, 2014] in HIV-1-infected, ART-naïve subjects. Initially, it will enrol subjects with a Screening HIV 1 RNA of 1000 to ≤100,000 c/mL, but recruitment may later be opened to subjects with a Screening HIV-1 RNA of 1000 to ≤500,000 c/mL. The selection of 500,000 c/mL as the Screening viral load cap is reasonable based on the response rates previously observed during short-term monotherapy with DTG and for 3TC. In the DTG Phase IIa dose-ranging study, subjects receiving monotherapy of DTG 50 mg once daily had a 2.5 log10 decline in HIV-1 RNA after 10 days of treatment [Min, 2011]. In early studies of HIV treatments, in which subjects were given 3TC monotherapy, a 1.5 log10 decline in HIV-1 RNA was observed over 2 weeks [Eron, 1995; Kuritzkes, 1996]. Thus, based on these levels of response, a 4 log10 decline in HIV-1 RNA could perhaps be achieved due to the combined activity of the two components. Starting with a viral load of 500,000 c/mL (5.7 log10 c/mL), a 4 log10 decline would result in HIV-1 RNA levels approximately at or less than 50 c/mL (1.7 log10 c/mL).

An identical sister study, 205543, will be conducted in parallel with Study 204861 in some countries. The overall objective of the clinical development program of DTG plus 3TC is to develop a FDC tablet.

2.2. Brief Background

A number of clinical studies have been published to date that provide supportive clinical data on the efficacy as well as favourable safety of two-drug first-line treatment regimens 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 subjects are extensive, with no resistance mutations being identified through 144 weeks of treatment (SINGLE, ING114467) [Walmsley, 2015; GlaxoSmithKline Document Number RM2007/00683/11]. 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.

Three randomised 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 enrol 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 [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 subjects 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].

Limited data are also available from two pilot studies to evaluate the dual regimen of DTG plus 3TC:

- An investigator-initiated 48-week pilot study, the PADDLE trial (NCT02211482), has been conducted in 20 HIV treatment-naïve subjects with no genotypic resistance to 3TC and a viral load of ≤100,000 c/mL at Screening and has provided notable early data on the efficacy of a once-daily DTG plus 3TC two-drug regimen. Subjects 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. By Week 8, all 20 subjects, including 4 subjects with a Baseline HIV-1 RNA of >100,000 c/mL, had reached a viral load of <50 c/mL and all maintained virologic suppression through Week 24 [Figueroa, 2015]. At Week 48, 18/20 (90%) of subjects achieved the primary endpoint of plasma HIV-1 RNA <50 copies/mL using the FDA snapshot algorithm for the intention to treat – exposed (ITT-E) population [Cahn, 2017].

- The ongoing ACTG A5353 trial is a Phase II, single-arm pilot study of once-daily DTG plus 3TC in treatment-naïve HIV-1-infected participants with a viral load of ≥1000 to <500,000 c/mL. Virologic efficacy (plasma HIV-1 RNA <50 c/mL using the FDA Snapshot) at Week 24 was 108/120 (90%) with no significant difference between the low (≤100,000 c/mL) and high (>100,000 c/mL) viral load strata: 90% and 89%, respectively [Taiwo, 2017].

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To demonstrate non-inferior antiviral activity of DTG + 3TC versus DTG + TDF/FTC at 48 weeks in HIV-1-infected, ART-naïve subjects	• Proportion of subjects with plasma HIV-1 RNA <50 copies/mL (c/mL) at Week 48 using the FDA Snapshot algorithm [Missing, Switch or Discontinuation = Failure (MSD=F)] for the intent-to-treat exposed (ITT-E) population
Secondary	
• To demonstrate the antiviral activity of DTG + 3TC versus DTG + TDF/FTC at 24, 96 and 144 weeks	• Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Weeks 24, 96 and 144 using the FDA Snapshot algorithm (MSD=F) for the ITT-E population
• To evaluate the antiviral activity, immunological effects, and incidence of disease progression (HIV-associated conditions, AIDS and death) of DTG + 3TC compared to DTG + TDF/FTC over time	• Time to viral suppression (HIV-1 RNA <50 c/mL); • Absolute values and changes from Baseline in CD4+ cell counts at Weeks 24, 48, 96 and 144; • Incidence of disease progression (HIV-associated conditions, AIDS and death).

Objectives	Endpoints
• To assess viral resistance in subjects meeting confirmed virologic withdrawal (CVW) criteria	• Incidence of treatment-emergent genotypic and phenotypic resistance to DTG and 3TC or TDF/FTC in subjects meeting CVW criteria
• To evaluate the safety and tolerability of DTG + 3TC compared to DTG + TDF/FTC over time	• Incidence and severity of adverse events (AEs) and laboratory abnormalities; • Proportion of subjects who discontinue treatment due to AEs over 24, 48, 96 and 144 weeks
• To evaluate renal biomarkers (in urine and blood) and bone biomarkers (in blood) in subjects treated with DTG + 3TC compared to DTG + TDF/FTC	• Change from Baseline in renal and bone biomarkers at Weeks 24, 48, 96 and 144
• To evaluate the effects of DTG + 3TC on fasting lipids compared to DTG + TDF/FTC over time	• Change from Baseline in fasting lipids at Weeks 24, 48, 96, and 144; • The incidence of Grade 2 or greater laboratory abnormalities in fasting LDL cholesterol by Weeks 24, 48, 96, and 144;
• To evaluate the effect of patient demographics and baseline characteristics (e.g. demographic factors, HIV-1 subtype, baseline CD4+ cell count) on response to DTG + 3TC compared to DTG + TDF/FTC over time	• Proportion of subjects by patient subgroup(s) (e.g. by age, gender, Baseline CD4+ cell count) with plasma HIV-1 RNA <50 c/mL at Weeks 24, 48, 96 and 144 using the Snapshot algorithm for the ITT-E population • Change from Baseline in CD4+ cell counts at Weeks 24, 48, 96 and 144 by patient subgroups
• To assess change in health-related quality-of-life for subjects treated with DTG plus 3TC compared to DTG + TDF/FTC	• Change from Baseline in health related quality of life using EQ-5D-5L at Weeks 4, 24, 48, 96, and 144 (or Withdrawal from the study)
Exploratory	
• To evaluate inflammation biomarkers in subjects treated with DTG+ 3TC compared to DTG + TDF/FTC	• Change from Baseline in inflammation biomarkers at Weeks 48, 96 and 144
• To evaluate telomere length in subjects treated with DTG + 3TC compared to DTG + TDF/FTC	• Change from Baseline in telomere length at Weeks 96 and 144

4. STUDY DESIGN

4.1. Overall Design

This study is a Phase III, randomised, double-blind, active-controlled, multicentre, parallel-group, non-inferiority study. The study will be conducted in approximately 700 HIV-1 infected, ART-naïve subjects with a Screening HIV-1 RNA of 1000 to ≤500,000 copies/mL (c/mL). Subjects will be randomised 1:1 to receive a two-drug regimen of

DTG plus 3TC once daily (approximately 350 subjects) or DTG plus the FDC tablet of TDF/FTC once daily (approximately 350 subjects). Subjects will be stratified by screening HIV-1 RNA (≤100,000 c/mL or >100,000 c/mL) and Screening CD4+ cell count (≤ or >200 cells/mm^3).

The study initially will enrol approximately 100 subjects with a Screening HIV-1 RNA of 1000 to ≤100,000 c/mL. Accumulated data from other clinical trials investigating the DTG plus 3TC dual regimen will undergo independent review. If the independent review is supportive of evaluating the dual regimen's efficacy in subjects with a Screening viral load of up to 500,000 c/mL, recruitment will be opened to subjects with a Screening HIV-1 RNA of 1000 to ≤500,000 c/mL. If the review does not support enrolment of such subjects, the Screening viral load will remain capped at ≤100,000 c/mL. This independent review of accumulated data on the DTG plus 3TC dual regimen was supportive, enabling an increase in the Screening viral load cap to ≤500,000 c/mL for subjects screened on/after 5 November 2016.

The study will comprise:

- a 28-day Screening Phase (which may be extended to 35 days to allow receipt of all Screening assessment results),
- a Double-blind Randomised Phase (Day 1 to Week 96),
- an Open-label Randomised Phase (Week 96 to Week 148), and
- a Continuation Phase (Figure 1).

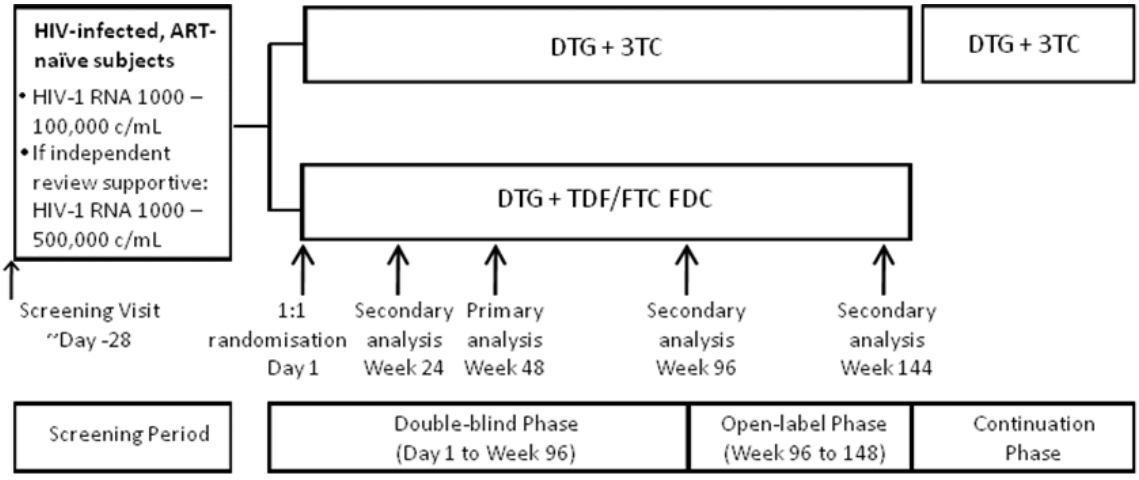
All subjects who successfully complete 96 weeks of randomised, blinded treatment will continue to receive their randomised treatment (DTG plus 3TC or DTG plus TDF/FTC FDC) in an open-label manner as part of the study through Week 148. Data from these subjects will provide long-term, comparative, descriptive information on durability of response, safety, and tolerability.

Subjects randomised to receive DTG plus 3TC who successfully complete 148 weeks of treatment may continue to have access to DTG plus 3TC in a Continuation Phase.

At Weeks 28, 52, 100, and 148, a confirmatory viral load measurement will be performed for subjects presenting with HIV-1 RNA ≥50 c/mL at the Week 24, 48, 96 and 144 visits, respectively. The primary and secondary efficacy endpoints correspond to viral load measurements collected within a ≤6 week window around the visits of interest (including data from the visits at Weeks 28, 52, 100, and 148), as per the FDA's Snapshot algorithm. For this reason, the primary and secondary analyses are denoted as occurring at Weeks 24, 48, 96 and 144 with the understanding that respective data from the Week 28, 52, 100 and 148 visits may be included.

Assuming a true response rate of 87% for the DTG plus 3TC arm and an 89% response rate for the DTG plus TDF/FTC arm at Week 48, the study requires 347 subjects per arm to have 90% power with a 10% non-inferiority margin and a 2.5% one-sided alpha level.

Figure 1 204861 Study Schematic



4.2. Treatment Arms and Duration

The study will be conducted in approximately 700 HIV-1 infected, ART-naïve individuals. Eligible subjects will be randomised 1:1 to receive DTG plus 3TC once daily or DTG plus TDF/FTC FDC once daily.

No dose reductions, modifications in dosage, or changes in the frequency of dosing will be allowed in this study, except those allowed and defined in the protocol.

The study will include a 28-day Screening Phase (which may be extended to 35 days to allow receipt of all Screening assessment results), a Double-blind Randomised Phase (Day 1 to Week 96), an Open-label Randomised Phase (Week 96 to Week 148), and a Continuation Phase (post-Week 148). If required by local regulations, subjects randomised to receive DTG plus 3TC once daily who successfully complete 148 weeks of treatment will continue to have access to DTG plus 3TC once daily in a 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 available, or
- the subject no longer derives clinical benefit, or
- the subject meets a protocol-defined reason for discontinuation, or
- development of the DTG plus 3TC dual regimen is terminated.

Subjects randomised to the DTG plus TDF/FTC FDC arm will receive DTG + TDF/FTC FDC through their Week 148 visit only, after which subjects will complete the study and will need to have alternate arrangements in place to access antiretroviral medication.

Subjects with ongoing AEs or laboratory abnormalities considered to be AEs will attend a Follow-up visit approximately four weeks after their last dose of study treatment.

Assessments at the Follow-up visit should reflect any ongoing complaints (e.g. blood draws to follow a laboratory abnormality). The Follow-Up visit is not required for successful completion of the study.

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 and sister study 205543. 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. Further, an interim futility analysis will be performed for the IDMC to evaluate the efficacy and safety of DTG plus 3TC when approximately 50% of subjects have completed their visit at Week 24; the sponsor will remain blinded to this analysis. Full details of the methods, timing, decision criteria and operating characteristics will be pre-specified in the IDMC Charter.

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

4.3. Type and Number of Subjects

Assuming a 26% screen failure rate, approximately 950 HIV-1-infected adult subjects will be screened to achieve approximately 700 randomised subjects to include approximately 350 subjects per treatment group.

The study initially will enrol approximately 100 subjects with a Screening HIV-1 RNA of 1000 to ≤100,000 c/mL. Accumulated data from other clinical trials investigating the DTG plus 3TC dual regimen will undergo independent review. If the independent review is supportive of evaluating the dual regimen's efficacy in subjects with a Screening viral load of up to 500,000 c/mL, recruitment will be opened to subjects with a Screening HIV-1 RNA of 1000 to ≤500,000 c/mL. If the review does not support enrolment of such subjects, the Screening viral load will remain capped at ≤100,000 c/mL. This independent review of accumulated data on the DTG plus 3TC dual regimen was supportive, enabling an increase in the Screening viral load cap to ≤500,000 c/mL for subjects screened on/after 5 November 2016.

A goal of this study is to target populations who are underrepresented in clinical studies, including approximately 15% women and approximately 15% subjects aged 50 years or older.

4.4. Design Justification

The use of randomised, active-controlled, double-blind, multicentre, parallel group, fully-powered non-inferiority studies as pivotal proof of safety and efficacy is a well established experimental design for establishing the non-inferiority of an investigational agent or regimen compared to an active comparator and is generally accepted at regulatory authorities as rigorous proof of antiviral activity [CDER, 2015]. The primary endpoint, proportion of subjects at Week 48 with plasma HIV-1 RNA below the assay limit of detection (e.g. <50 c/mL), is also a very well-established surrogate endpoint for prognosis of HIV-1 infection and disease progression [CDER, 2015].

A number of clinical studies to date have provided supportive clinical data on the efficacy as well as favourable safety of two-drug first-line treatment regimens that include a boosted PI or an INSTI (see Section 2.2).

The comparator regimen, DTG plus TDF/FTC, has been established as one of the preferred first-line treatment regimens for treatment-naïve HIV infected subjects and is recognised as such, as evidenced by its wide acceptance in treatment guidelines [BHIVA, 2015; DHHS, 2016; EACS, 2015; IAS-USA, 2014].

Considering these points above, the proposed study design should allow a thorough assessment of the DTG plus 3TC regimen.

4.5. Dose Justification

The efficacy, PK, safety, and drug interaction potential of DTG, 3TC, TDF and FTC as individual agents and of TDF/FTC FDC have been evaluated in extensive clinical development programmes. DTG, 3TC and TDF/FTC FDC are approved and marketed as TIVICAY 50 mg once daily, EPIVIR 300 mg once daily, and Truvada 300 mg/200 mg once daily respectively, the doses used in the current study.

4.6. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with DTG and 3TC can be found in the DTG Investigator's Brochure (IB) [GlaxoSmithKline Document Number RM2007/00683/11] and DTG and 3TC product labels. The following section outlines the risk assessment and mitigation strategy primarily for DTG in this protocol. For 3TC and TDF/FTC, the approved country product labels should be referenced. The comparator regimen, DTG plus TDF/FTC, has been established as a preferred first line treatment regimen for treatment-naïve HIV infected subjects and is recognised as such, as evidenced by it wide acceptance in treatment guidelines [BHIVA, 2015; DHHS; 2016; EACS, 2015; IAS-USA, 2014].

4.6.1. Risk Assessment

The following table outlines the risk assessment and mitigation strategy for this protocol.

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy[a]
Investigational Product (IP) [DTG, 3TC, TDF/ FTC] Refer to DTG IB and country product labels 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.	Subjects with history of allergy/sensitivity to any of the study drugs are excluded (Section 5.2). Specific/detailed toxicity management guidance is provided for HSR (Section 12.8.1.5) and rash (Section 12.8.1.6). The subject informed consent form includes information on this risk and the actions subjects 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, subjects 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	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 subjects 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 subjects, likely contributed to significant elevations in liver chemistries. Current treatment guidelines [DHHS, 2016; EACS, 2015] do not recommend monotherapy with 3TC for patients with HBV infection, which is what subjects randomised to DTG plus 3TC, would effectively be receiving. Emergence of	Subjects meeting either of the following criteria during the screening period are excluded from participating (Section 5.2). • Alanine aminotransferase (ALT) ≥5 times the upper limit of normal (ULN) or ALT ≥3x ULN and bilirubin ≥1.5x ULN (with >35% direct bilirubin); • Subjects positive for Hepatitis B surface antigen (HBsAg); subjects 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; • Subjects 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

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy[a]
Investigational Product (IP) [DTG, 3TC, TDF/ FTC] Refer to DTG IB and country product labels for additional information		
	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 subjects can result in severe exacerbations of hepatitis B.	drug:drug interactions with study treatment throughout the entire study period. Specific/detailed liver stopping criteria and toxicity management guidance is provided for suspected DILI or other clinically significant liver chemistry elevations (Appendix 3, Section 12.3).
DTG: Psychiatric disorders	Psychiatric disorders including suicidal ideation and behaviours are common in HIV-infected patients. The psychiatric profile for DTG (including suicidality, depression, bipolar and hypomania, anxiety and abnormal dreams) was similar to RAL- or favourable 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.	Subjects who in the investigator's judgment, pose a significant suicidality risk, are excluded from participating (Section 5.2). 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 subjects who experience signs of suicidal ideation or behaviour (Section 7.4.6). The subject informed consent form includes information on this risk of depression and suicidal ideation and behaviours.

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy[a]
Investigational Product (IP) [DTG, 3TC, TDF/ FTC] Refer to DTG IB and country product labels for additional information		
DTG and 3TC: Increased rates of virologic failure/ observed resistance	Lower responses in subjects 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]. 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 subjects. 3TC: M184V is a common single mutation that leads to full resistance to 3TC.	Subjects with evidence of primary viral resistance based on the presence of any major resistance-associated mutation (including M184V) are excluded from this study (Section 5.2). The study will initially enrol subjects with a Screening HIV 1 RNA of 1000 to ≤100,000 c/mL. Following an independent review of clinical data on the DTG plus 3TC treatment regimen, the Screening viral load cap may be increased to 500,000 c/mL. The viral load cap will maximise the opportunity for subjects randomised to the DTG plus 3TC arm to rapidly achieve an undetectable viral load (HIV-1 RNA <50 c/mL), which may help minimise the potential for emergent drug resistance that could result in functional DTG monotherapy (i.e. if the M184V mutation arises, conferring 3TC resistance). Subjects will have HIV-1 RNA measured at each study visit. An IDMC will be instituted to ensure external objective medical and/or statistical review of efficacy and safety (Section 10.8). 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 9.3.4).
DTG: Theoretical serious drug interaction with dofetilide and pilsicainide	Co-administration of DTG may increase dofetilide/pilsicainide plasma concentration via inhibition of organic cation transporter 2 (OCT2), resulting in potentially life-threatening toxicity.	The co-administration of DTG with dofetilide or pilsicainide is prohibited in the study (Section 6.9.2).

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy[a]
Investigational Product (IP) [DTG, 3TC, TDF/ FTC] Refer to DTG IB and country product labels for additional information		
DTG, 3TC, and TDF/FTC: 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, TDF and FTC are eliminated by renal excretion and exposures increase in patients with renal dysfunction. Renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of TDF in clinical practice.	Due to requirements for dose reduction of 3TC or dose interval adjustments of TDF/FTC in patients with renal dysfunction, subjects with a creatinine clearance (CrCL) <50 mL/min/1.73 m^2 are excluded (Section 5.2). CrCl is calculated in all patients prior to initiating therapy and renal function (creatinine clearance and serum phosphate) will be monitored at all subsequent study visits. Specific/detailed toxicity management guidance is provided for subjects who develop a decline in renal function/proximal renal tubule dysfunction (PRTD) (Section 12.8.1.3) or proteinuria (Section 12.8.1.4).
DTG: Creatine Phosphokinase (CPK) elevations	Asymptomatic CPK elevations mainly in association with exercise have been reported with DTG therapy.	Specific detailed toxicity management guidance is provided for subjects who develop Grade 3 to 4 CPK elevations (Section 12.8.1.8).

a. Careful monitoring of events will be conducted using serious adverse event (SAE) reports and alerts for Grade 3/4 laboratory toxicities (per Division of Acquired Immune Deficiency Syndrome [DAIDS] toxicity gradings for HIV-infected patients). Serious/severe events will be managed appropriately including, but not limited to, withdrawal of study drug, and will be followed to resolution as per Sponsor's standard medical monitoring practices.
Clinical Safety Data will be routinely reviewed in GlaxoSmithKline (GSK) Safety Review Team meetings. This will include in-stream review of data from this clinical trial on a routine basis, review of aggregate data on a protocol and program basis when available, and review of competitor data from the literature.

4.6.2. 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 ART agents. DTG 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 2.2). Results from these trials pave the way for the exploration of other dual-therapy strategies, such as DTG plus 3TC, a regimen of two well-characterised antiretrovirals that may provide 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.

4.6.3. Overall Benefit:Risk Conclusion

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

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the ViiV Healthcare investigational product or other study treatment that may impact subject eligibility is provided in the DTG IB and the respective product labels.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects are allowed to re-screen for this study one time, except where exclusionary HIV-1 resistance was present; re-screening will require a new subject 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 following are study specific eligibility criteria unless stated otherwise. In addition to these criteria, Investigators must exercise clinical discretion regarding selection of

appropriate study subjects, taking into consideration any local treatment practices or guidelines and good clinical practice (GCP).

5.1. Inclusion Criteria

Eligible subjects 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. no active substance abuse, acute major organ disease, or planned long-term work assignments out of the country).

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

AGE
1. HIV-1 infected adults ≥18 years of age (or older, if required by local regulations), at the time of signing the informed consent.

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Screening plasma HIV-1 RNA of 1000 c/mL to ≤100,000 c/mL. If an independent review of accumulated data from other clinical trials investigating the DTG plus 3TC dual regimen is supportive of the DTG plus 3TC treatment regimen, enrolment will be opened to subjects with Screening plasma HIV-1 RNA of 1000 c/mL to ≤500,000 c/mL; 3. Antiretroviral-naïve (defined as ≤10 days of prior therapy with any antiretroviral agent following a diagnosis of HIV-1 infection). Subjects 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 >1 year from HIV diagnosis or there is documented HIV seronegativity between the last prophylactic dose and the date of HIV diagnosis.

SEX
4. Male or female. A female subject 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 test at Baseline), not lactating, and at least one of the following conditions applies: a. Non-reproductive potential defined as: • Pre-menopausal females with one of the following:

- Documented tubal ligation
- Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
- Hysterectomy
- Documented Bilateral Oophorectomy

- Postmenopausal defined as 12 months of spontaneous amenorrhea and ≥45 years of age [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and oestradiol levels consistent with menopause is confirmatory (refer to laboratory reference ranges for confirmatory levels)]. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment.

b. Reproductive potential and agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see Appendix 9, Section 12.9.1) from 30 days prior to the first dose of study medication and until the last dose of study medication and completion of the Follow-up visit.

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

All subjects 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
5. Subject or the subject's legal representative capable of giving signed informed consent as described in Section 10.2 which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

OTHER
6. **Subjects enrolled in France**: A subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

CONCURRENT CONDITIONS/MEDICAL HISTORY
1. Women 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 disease [CDC, 2014], except cutaneous Kaposi's sarcoma not requiring systemic therapy and historical or current CD4 cell counts less than 200 cells/mm^3. 3. Subjects with severe hepatic impairment (Class C) as determined by Child-Pugh classification (Appendix 2, 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: • Subjects positive for HBsAg are excluded; • Subjects negative for anti-HBs but positive for anti-HBc (negative HBsAg status) and positive for HBV DNA are excluded. NOTE: Subjects 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. 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). Subjects who are at least 14 days post completed treatment are eligible. 8. History or presence of allergy or intolerance to the study drugs or their components or drugs of their class; 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 localised malignancies require agreement between the investigator and the Study Medical Monitor for inclusion of the subject. 10. Subjects who in the investigator's judgment, poses a significant suicidality risk. Recent history of suicidal behaviour 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, except recognised ART as allowed above (inclusion criterion 3.), with documented activity against HIV-1 *in vitro* within 28 days of first dose of study treatment; 14. 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. 15. **Subjects enrolled in France (and other countries as required by local regulations or ethics committees/IRBs)**: the subject has participated in any study using an investigational drug during the previous 60 days or 5 half-lives, or twice the duration of the biological effect of the experimental drug or vaccine, whichever is longer, prior to screening for the study or the subject will participate simultaneously in another clinical study.

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 [IAS-USA, 2014] 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 subject'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 via the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) method.

5.3. Screening Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomised. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events (see Section 7.4.1.6).

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

5.4. Withdrawal/Stopping Criteria

Subjects permanently discontinuing study treatments prior to Week 148 are considered to be withdrawn from the study treatments and also from the study.

A subject 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 subject 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 subjects will not be replaced.

Subjects 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 subjects who withdraw from the study.

Subjects 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.

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

- Subject or Investigator non-compliance;
- At the request of the subject, Investigator, GSK or ViiV Healthcare;
- The subject requires concurrent prohibited medications during the course of the study. The subject 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 subject.

Subjects <u>must</u> be discontinued from the study for any of the following reasons:

- CVW criteria as specified in Section 5.4.1.3 are met;
- Subject requires substitution or dose modification of DTG, 3TC, TDF or FTC;
- Liver toxicity where stopping criteria specified in Section 5.4.2 and Appendix 3, Section 12.3 are met and no compelling alternate cause is identified;
- Renal toxicity criteria as specified in Appendix 8, Section 12.8.1.3 are met and no compelling alternate cause is identified;
- Grade 4 clinical AE considered causally related to study drug (Appendix 8, Section 12.8.1);
- Allergic reaction or rash criteria as specified in Appendix 8 (Section 12.8.1.5 and Section 12.8.1.6, respectively) are met and no compelling alternate cause is identified;

- Pregnancy (intrauterine), regardless of termination status of pregnancy (Section 7.4.2).

If a subject is prematurely or permanently withdrawn from the study, the procedures described in the Time and Events Table (Section 7.1) for the Withdrawal visit – and if necessary the Follow Up visit – are to be performed.

A Follow-up visit may occur approximately 4 weeks after the last dose of study treatment and is only required in subjects with ongoing clinical or laboratory AEs at the time of Withdrawal. All data from the Withdrawal visit will be recorded, as they comprise an essential evaluation that should be done prior to discharging any subject from the study.

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

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

5.4.1. Virologic Criteria for Subject 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 in Section 5.4.1.1 wherein the virologic withdrawal criteria revolve around the HIV-1 RNA cut-off of 200 c/mL.

5.4.1.1. Virologic Withdrawal Criteria

Suspected Virologic Withdrawal criteria

A single HIV-1 RNA value as defined by Virologic Non-response or Virologic Rebound 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 two and four weeks after the subject met a SVW criterion unless a delay is necessary to meet the requirements of confirmatory HIV-1 RNA testing as described in Section 5.4.1.2. 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 $\log_{10}$ c/mL by Week 12, with subsequent confirmation, unless plasma HIV-1 RNA is <200 c/mL.
- Confirmed plasma HIV-1 RNA levels ≥200 c/mL on 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.

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

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

5.4.1.2. Managing Subjects 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 subject's HIV-1 RNA plasma level qualifies him/her as meeting an SVW criterion, the Investigator should query the subject 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 two 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 subject should receive full doses of all study drugs.
- Confirmatory testing should be scheduled at least 4 weeks following any immunisation, during which time the subject should receive full doses of study drugs.

- If therapy is interrupted due to toxicity management, non-compliance, or other reasons, confirmatory testing should be scheduled 2 to 4 weeks following resumption of full doses of study drugs.
- The subject 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 subjects, whenever necessary.

5.4.1.3. Managing Subjects Meeting Confirmed Virologic Withdrawal Criteria

Once a subject has been confirmed as meeting a virologic withdrawal criterion, a '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.

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

The protease (PRO)/reverse transcriptase (RT)/integrase assays used in this study are not validated for plasma HIV-1 RNA levels <500 c/mL. Nevertheless, for all subjects who meet CVW Criteria, additional plasma samples will be analysed in an attempt to obtain genotype/phenotype data on as many samples as possible. Subjects 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 subjects.

If a subject 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 7.1). These data will be recorded, as they comprise an essential evaluation that needs to be done before discharging any subject from the study.

5.4.1.4. Managing subjects with HIV-1 RNA ≥ 50 c/mL at Weeks 24, 48, 96 and 144

At Weeks 24, 48, 96 and 144 (key study endpoint visits) repeat HIV-1 RNA testing is required for any HIV-1 RNA ≥50 c/mL and must be performed at the Week 28, Week 52, Week 100 and Week 148 study visits respectively, so long as the guidelines provided above for scheduling confirmatory HIV-1 RNA assessment to avoid false-positive results have been followed.

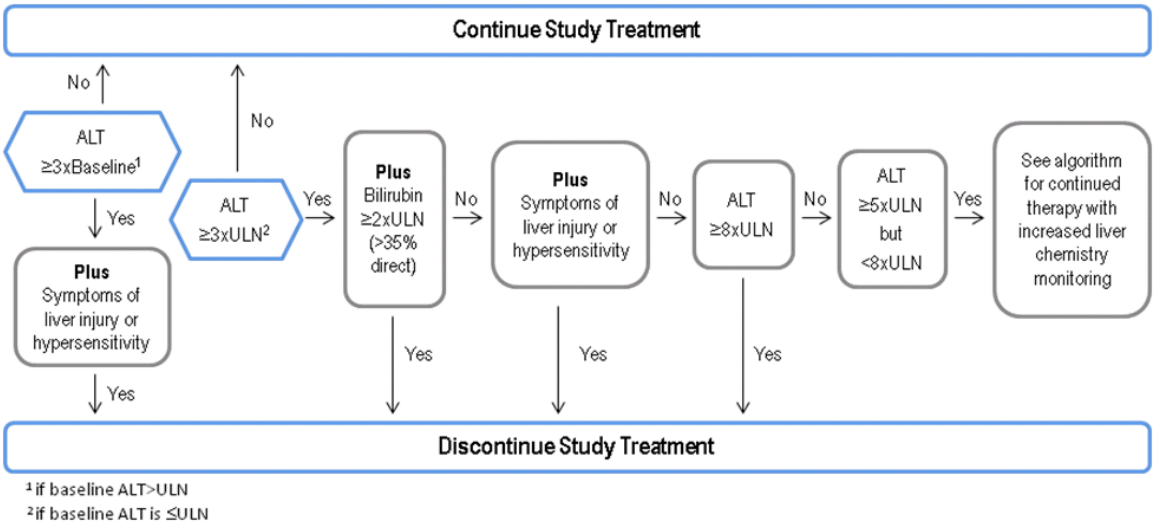
NOTE: Subjects whose HIV-1 RNA is <50 c/mL at Weeks 24, 48 and 96 will not attend the Week 28, Week 52 and Week 100 study visits, respectively.

5.4.2. Liver Chemistry Stopping Criteria

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

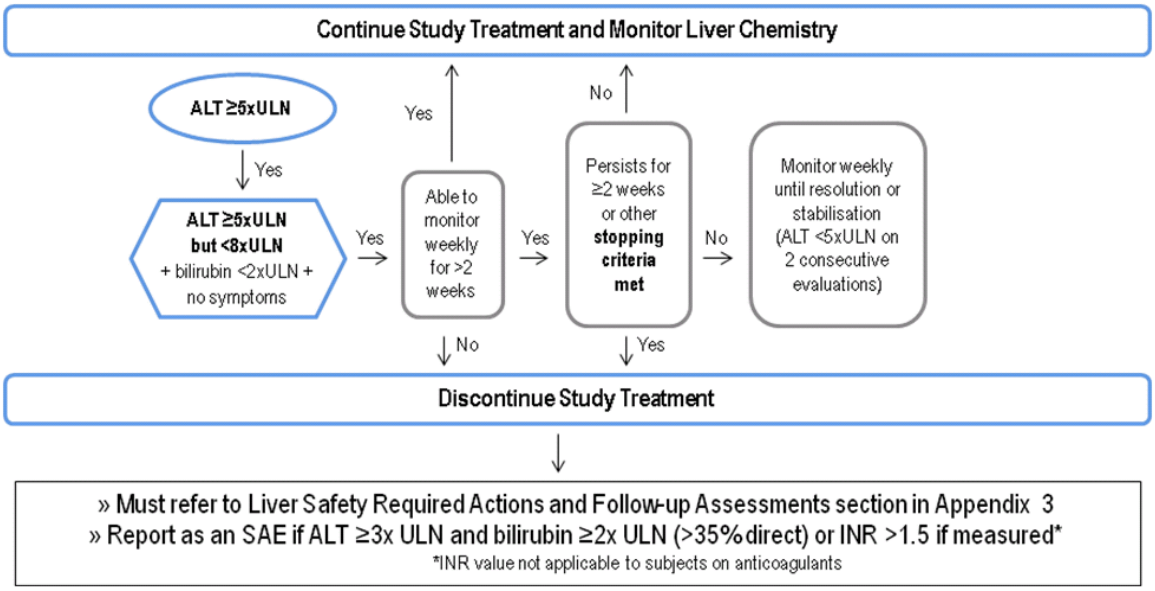
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Liver Chemistry Stopping and Increased Monitoring Algorithm



» Must refer to Liver Safety Required Actions and Follow-up Assessments section in Appendix 3
» Report as an SAE if ALT ≥3x ULN and bilirubin ≥2x ULN (>35% direct) or INR >1.5 if measured*
*INR value not applicable to subjects on anticoagulants

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 Appendix 3, Section 12.3.

5.4.2.1. Study Treatment Restart

If a subject meets liver chemistry stopping criteria do not restart the subject 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 is signed by the subject.

Refer to Appendix 4, Section 12.4 for full guidance.

5.5. Subject and Study Completion

Subjects are considered to have completed the study if they satisfy one of the following:

- Randomly assigned to either treatment arm, completed the Open-label Randomised Phase including the Week 148 visit, and did not enter the Continuation Phase;
- Randomly assigned to DTG plus 3TC, completed the Open-label Randomised Phase including the Week 148 visit, entered and completed the Continuation Phase (defined as remaining on study 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 available or development of the DTG plus 3TC dual regimen is terminated).

Subjects with ongoing AEs or laboratory abnormalities considered to be AEs will attend a Follow-up visit approximately four weeks after their last dose of study treatment. The Follow-up visit is not required for successful completion of the study.

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

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

The term 'study treatment' is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

	Study Treatment (Double-blind Randomised Phase, Day 1 to Week 96)		
Product name:	Dolutegravir, DTG	Lamivudine, 3TC	Tenofovir disoproxil fumarate/emtricitabine fixed-dose combination, TDF/FTC FDC
Formulation description:	Commercial supply or Clinical trial material, which is the same formulation as the commercial material with the exception of the film coat colour	Over-encapsulated commercial supply tablet to visually match over-encapsulated TDF/FTC FDC tablet	Over-encapsulated commercial supply tablet to visually match over-encapsulated 3TC tablet
Dosage form:	Tablet	Capsule	Capsule
Unit dose strength(s)/Dosage level(s):	50 mg	300 mg	300 mg TDF/200 mg FTC
Route of Administration:	Oral	Oral	Oral
Dosing instructions:	Take one tablet once daily with or without food	Take one capsule once daily with or without food	Take one capsule once daily with or without food
Physical description:	Commercial supply: Yellow, round, film-coated, biconvex tablets debossed with “SV 572” on one side and “50” on the other side. The tablets are packaged into HDPE bottles with induction seals and child-resistant closures, each containing 30 tablets. Clinical trial supply: White, round, biconvex, film-coated tablets debossed on one side with “SV 572” and on the other side with “50”. The tablets are packaged into high density polyethylene (HDPE) bottles with induction seals and child-resistant closures. Each 45 ml bottle contains 30 tablets and a desiccant.	Swedish Orange, size AA elongated double-blind hydroxypropyl methylcellulose (HPMC) capsules. The capsules are packaged into HDPE bottles with induction seals and child- resistant closures. Each 150 mL bottle contains 30 capsules and a desiccant.	Swedish Orange, size AA elongated double-blind HPMC capsules. The capsules are packaged into HDPE bottles with induction seals and child-resistant closures. Each 150 mL bottle contains 30 capsules and a desiccant.

	Study Treatment (Open-label Randomised Phase, Week 96 to Week 148)		
Product name:	Dolutegravir, DTG	Lamivudine, 3TC	Tenofovir disoproxil fumarate/emtricitabine fixed-dose combination, TDF/FTC FDC
Formulation description:	Commercial supply or Clinical trial material, which is the same formulation as the commercial material with the exception of the film coat colour	Commercial supply	Commercial supply
Dosage form:	Tablet	Tablet	Tablet
Unit dose strength(s)/Dosage level(s):	50 mg	300 mg	300 mg TDF/200 mg FTC
Route of Administration:	Oral	Oral	Oral
Dosing instructions:	Take one tablet once daily with or without food	Take one tablet once daily with or without food	Take one tablet once daily with or without food
Physical description:	Commercial supply: Yellow, round, film-coated, biconvex tablets debossed with “SV 572” on one side and “50” on the other side. The tablets are packaged into HDPE bottles with induction seals and child-resistant closures, each containing 30 tablets. Clinical trial supply: White, round, biconvex, film-coated tablets debossed on one side with “SV 572” and on the other side with “50”. The tablets are packaged into HDPE bottles with induction seals and child-resistant closures. Each 45 ml bottle contains 30 tablets and a desiccant.	Gray, diamond-shaped, film-coated tablets engraved with “GX EJ7” on one side and plain on the reverse side. The tablets are packed into HDPE bottles with child-resistant closures each containing 30 tablets.	Blue, capsule-shaped, film-coated tablet, debossed on one side with “GILEAD” and on the other side with “701”. The tablets are packed in over-labelled HDPE bottles with polypropylene child-resistant closures each containing 30 tablets and a desiccant.

	Study Treatment (Continuation Phase)	
Product name:	Dolutegravir, DTG	Lamivudine, 3TC
Formulation description:	Commercial supply or Clinical trial material, which is the same formulation as the commercial material with the exception of the film coat colour	Commercial supply
Dosage form:	Tablet	Tablet
Unit dose strength(s)/Dosage level(s):	50 mg	300 mg
Route of Administration:	Oral	Oral
Dosing instructions:	Take one tablet once daily with or without food	Take one tablet once daily with or without food
Physical description:	Commercial supply: Yellow, round, film-coated, biconvex tablets debossed with "SV 572" on one side and "50" on the other side. The tablets are packaged into HDPE bottles with induction seals and child-resistant closures, each containing 30 tablets. Clinical trial supply: White, round, biconvex, film-coated tablets debossed on one side with "SV 572" and on the other side with "50". The tablets are packaged into HDPE bottles with induction seals and child-resistant closures. Each 45 ml bottle contains 30 tablets and a desiccant.	Gray, diamond-shaped, film-coated tablets engraved with "GX EJ7" on one side and plain on the reverse side. The tablets are packed into HDPE bottles with child-resistant closures each containing 30 tablets.

6.2. Treatment Assignment

Informed consent must be obtained prior to any study procedures, including any screening assessment. Subjects will be assigned to study treatment in accordance with the computer-generated randomisation schedule. The central randomisation schedule will be generated by PPD using a validated SAS developed program.

Randomisation and study treatment assignment 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 register subjects. Subjects will be randomized in a 1:1 ratio to DTG plus 3TC or DTG plus TDF/FTC FDC in accordance with the computer-generated randomisation schedule. Each subject will be assigned a unique identifier (designating the subject's randomisation

code) and a unique treatment number, which matches the randomised treatment assignment.

Subjects will maintain the assigned treatment group throughout both the Double-blind Randomised Phase (Day 1 to Week 96) and the Open-label Randomised Phase (Week 96 to Week 148).

Subjects who are randomly assigned into the study and subsequently withdrawn may not be rescreened. Once a randomisation number has been assigned it must not be re-assigned.

6.3. Blinding

Participants and investigators will remain blinded during the Double-blind Randomised Phase. The sponsor will be unblinded at Week 24 in order to provide results from the 24-week interim analysis to regulatory authorities but no external dissemination of results will occur until at least all the patients are through the primary time point, i.e. Week 48.

Subjects will receive open-label DTG plus double-blinded 3TC or open-label DTG plus double-blinded TDF/FTC FDC therapy during the Double-blind Randomised Phase (i.e. through their Week 96 study visit). Study treatment during the Open-label Randomised Phase after Week 96 up to Week 148 will be unblinded.

6.3.1. Emergency Unblinding

- The investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the investigator.
- Investigators have direct access to the subject's individual study treatment.
- It is preferred (but not required) that the investigator first contacts the Medical Monitor or appropriate ViiV Healthcare/GSK/PPD study personnel to discuss options **before** unblinding the subject's treatment assignment.
- If ViiV Healthcare/GSK/PPD personnel are not contacted before the unblinding, the investigator must notify ViiV Healthcare/GSK/PPD as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study.
- The date and reason for the unblinding must be fully documented in the case report form (CRF).

A subject will be withdrawn if the subject's treatment code is unblinded by the investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the CRF.

- GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the

report, identifying the subject's treatment assignment, may be sent to investigators in accordance with local regulations and/or ViiV Healthcare/GSK policy.

6.3.2. Scheduled Unblinding

Investigators will unblind all subjects to study treatment as they complete the Week 96 visit (see Section 7.1) prior to subjects entering the Open-label Randomised Phase (Week 96 to Week 148).

6.4. Packaging and Labeling

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

6.5. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required.

- 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 subjects enrolled in the study may receive study treatment and only authorised site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the Study Reference Manual (SRM).
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
- A 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.

6.6. Compliance with Study Treatment Administration

Study treatment accountability will be evaluated using pill counts of unused study treatments (DTG plus 3TC or DTG plus TDF/FTC FDC). This assessment will be conducted each time the subject receives a new (refill) supply of study treatments through the Withdrawal visit or study completion. These data will be recorded in the subject's CRF but will not be summarised for analysis purposes.

6.7. Treatment of Study Treatment Overdose

For this double-blind study, any tablet intake exceeding the randomised daily number of tablets for study treatment will be considered an overdose (see [TIVICAY Product Information, 2017]; [EPIVIR Product Information, 2017]; [Truvada Product Information, 2017]). 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 12.7.1) 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 12.7.2).

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.

6.8. Treatment after the End of the Study

Prior to completion of the Week 148 visit, randomised subjects will need to have alternative arrangements in place for access to antiretroviral medication. If required by local regulations, subjects randomised to receive DTG plus 3TC once daily therapy and who have successfully completed both the 96 weeks of treatment in the Double-blind Randomised Phase and the Open-label Randomised Phase through Week 148 will be given the opportunity to continue to receive DTG plus 3TC once daily (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 available, or
- the subject no longer derives clinical benefit, or
- the subject meets a protocol-defined reason for discontinuation, or
- development of the DTG plus 3TC dual regimen is terminated.

Subjects randomised to the DTG plus TDF/FTC FDC arm will receive DTG plus TDF/FTC FDC through their Week 148 visit only, after which subjects will complete the study and will need to have alternate arrangements in place to access antiretroviral medication.

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

6.9. Concomitant Medications and Non-Drug Therapies

Subjects 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, especially if any new concomitant medications are reported by subjects. All concomitant medications taken during the study will be recorded in the eCRF. The minimum requirement is that the drug name, route, and the dates of administration are to be recorded.

6.9.1. 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 6.9.2). Chemoprophylaxis for HIV-associated conditions is encouraged, if appropriate, at the discretion of the subject 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 minimise the risk of non-specific increases in the level of HIV-1 plasma RNA at the next scheduled assessment.

DTG plus 3TC and DTG plus TDF/FTC FDC should be administered 2 hours before OR 6 hours after taking polyvalent cation-containing antacids. Proton pump inhibitors and H2-antagonists may be used in place of antacids with no scheduling restrictions. Concurrent administration with multivitamins is acceptable. Calcium or iron supplements can be taken with study treatment provided that all are taken together with a meal. Under fasted conditions, DTG 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 with metformin, to maintain glycaemic control.

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

6.9.2. Prohibited Medications and Non-Drug Therapies

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

- HIV immunotherapeutic vaccines (see Section 6.9.1 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 5.2).
- Systemically administered immunomodulators (such as interleukin and interferon agents) are prohibited through Week 148 (a list of examples is provided in the SRM).

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 of the Double-blind Randomised Phase; 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.
- 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.

- Carbamazepine
- Oxcarbamazepine
- Phenobarbital
- Phenytoin
- Rifampicin or rifapentine
- St. John's wort (*Hypericum perforatum*)

Dofetilide and pilsicainide are prohibited as DTG may inhibit their renal tubular secretion resulting in increased dofetilide/pilsicainide 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. STUDY ASSESSMENTS AND PROCEDURES

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

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table, Section 7.1.

7.1. Time and Events Table

Procedures	Screening Visit[a]	Double-blind Randomised Phase													Open-label Randomised Phase						Continuation Phase[c]	Withdrawal	Follow-up[d]
		Baseline / Day 1	Week 4	8	12	16	24	28[b]	36	48	52[b]	60	72	84	96	100[b]	108	120	132	144	148	Every 12 weeks after Week 148		
Clinical and Other Assessments																								
Written informed consent	X																							
Inclusion/Exclusion criteria[e]	X	X																						
Demography	X																							
Prior ART history	X																							
Medical history[f]	X																							
Current medical conditions	X																							
Cardiovascular risk assessment, including vital signs[g]	X													X					X					
HIV risk factors and mode of transmission		X																						
CDC HIV-1 classification	X	X																						
HIV associated conditions			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Columbia Suicidality Severity Rating Scale		X[h]	X	X	X	X	X		X	X		X	X	X	X		X	X	X	X		X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Symptom Directed Physical Exam/Medical Decision Making[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
12-lead ECG[j]	X																							

Procedures	**Screening Visit**[a]	**Double-blind Randomised Phase**														**Open-label Randomised Phase**						**Continuation Phase**[c]	**Withdrawal**	**Follow-up**[d]
		Baseline / Day 1	**Week**																					
			4	**8**	**12**	**16**	**24**	**28**[b]	**36**	**48**	**52**[b]	**60**	**72**	**84**	**96**	**100**[b]	**108**	**120**	**132**	**144**	**148**	**Every 12 weeks after Week 148**		
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious adverse events	X[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EQ-5D-5L[l]		X	X				X			X					X					X			X	
Laboratory Assessments																									
Plasma for HIV genotyping	X																								
Quantitative plasma HIV-1 RNA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[m]	X	X	
Lymphocyte subset	X	X	X	X	X	X	X		X	X		X	X	X	X		X	X	X	X	X		X	
Plasma for storage/inflammation biomarkers[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical chemistry	X	X	X	X	X	X	X		X	X		X	X	X	X		X	X	X	X	X		X	X
Haematology	X	X	X	X	X	X	X		X	X		X	X	X	X		X	X	X	X	X		X	X
PT/INR	X																							
Fasting lipids and glucose[o]		X					X			X					X					X			X[p]	
Urinalysis and spot urine for protein analysis[q]		X					X			X					X					X			X	X
Pregnancy test[r]	S	U	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	
HBsAg, anti-HBc, anti-HBs, and HBV DNA[s]	X																								
HCV antibody	X																								
RPR	X																								

Procedures	**Screening Visit**[a]	**Double-blind Randomised Phase**														**Open-label Randomised Phase**						**Continuation Phase**[c]	**Withdrawal**	**Follow-up**[d]
		Baseline / Day 1	**Week**																					
			4	**8**	**12**	**16**	**24**	**28**[b]	**36**	**48**	**52**[b]	**60**	**72**	**84**	**96**	**100**[b]	**108**	**120**	**132**	**144**	**148**	**Every 12 weeks after Week 148**		
Renal and bone marker analytes (blood/urine)[t]		X					X			X					X					X			X	
Whole blood for virology/telomere length[u]		X[u]																			X[u]		X[u]	
Whole blood for telomere length[v]															X					X				
Study Treatment																								
IVRS/IWRS[w]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study treatment		X	X	X	X	X	X		X	X		X	X	X	X		X	X	X	X	X	X		
Study treatment accountability (pill counts)			X	X	X	X	X		X	X		X	X	X	X		X	X	X	X	X	X	X	

anti-HBc = antibody to hepatitis B core antigen, anti-HBs = hepatitis B surface antibody, ART = antiretroviral therapy, CDC = Centers for Disease Control and Prevention, DNA = deoxyribonucleic acid, ECG = electrocardiograph, HBsAg = hepatitis B surface antigen, HCV = hepatitis C virus, HIV-1 = human immunodeficiency virus type 1, INR = international normalised ratio, IVRS = interactive voice recognition system, IWRS = interactive web recognition system, PT = prothrombin time, RNA = ribonucleic acid, RPR = rapid plasma reagin

a. Randomisation may occur as soon as all Screening results are available.

b. Subjects with plasma HIV-1 RNA levels ≥50 c/mL at Week 24, Week 48 and Week 96 must have HIV-1 levels re-assessed by a second measurement performed four weeks later at the Week 28, Week 52 visit and Week 100 visit, respectively. Subjects should have received full doses of study treatment for at least 2 weeks at the time of HIV-1 RNA re-assessment for any HIV-1 RNA level ≥50 c/mL. Subjects with plasma HIV-1 RNA levels <50 c/mL at Week 24, Week 48 and Week 96 should not attend the Week 28 visit, Week 52 visit and Week 100 visit, respectively.

c. Subjects randomised to DTG plus 3TC who complete through Week 148 may enter the Continuation Phase. Subjects completing the Continuation Phase must return to the clinic for an End of Continuation Phase visit when transitioning to commercial supplies or to an alternate ART regimen if appropriate. At this visit, conduct study assessments as specified for all Continuation Phase visits with the exception of dispensing study treatment.

d. An in-clinic Follow-up visit will be conducted 4 weeks after the last dose of study medication for subjects with the following conditions at the last on-study visit: ongoing AEs, serious adverse events (SAEs) regardless of attributability, any laboratory abnormalities considered to be AEs or potentially harmful to the subject.

e. 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.
f. Full medical history will be conducted prior to randomisation 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.
g. At Screening, assessment for cardiovascular risk will include height, weight, blood pressure, smoking status and history, pertinent medical conditions (e.g., hypertension, diabetes mellitus), and family history of premature cardiovascular disease. Body mass index (BMI) will be calculated within the eCRF. At Week 96 and Week 144, only weight will be measured.
h. On Day 1, the electronic Columbia Suicidality Severity Rating Scale (eC-SSRS) is to be administered prior to randomisation.
i. Limited physical examination to include blood pressure at Day 1 (recorded in eCRF) for Framingham score assessment. Blood pressure to be measured after resting in a semi-supine position for at least 5 minutes.
j. A 12-lead ECG will be performed after resting in a semi-supine position for at least 5 minutes.
k. Only SAEs related to study participation or to a concomitantly administered ViiV Healthcare/GSK product will be collected between obtaining informed consent and administration of study drug at Day 1.
l. The questionnaire is recommended to be administered at the beginning of the visit before any other assessments are conducted. Only conduct the questionnaire at Withdrawal if occurring prior to Week 144.
m. At Week 148, repeat HIV-1 RNA testing will only be performed for subjects with HIV-1 RNA $\geq$50 c/mL at Week 144.
n. Plasma samples for storage will be collected at each visit, including unscheduled visits (e.g. for HIV-1 RNA levels and immunological parameters). Additionally, these samples will be used when needed such as when samples are lost or arrive at the laboratory unevaluable or as a priority need for genotypic and/or phenotypic analyses when subjects meet CVW criteria. Additionally, inflammation biomarkers (Interleukin-6 [IL-6], high-sensitivity C-reactive protein [hs-CRP]) will be measured at Day 1, Week 48, Week 96 and Week 144 using stored plasma samples.
o. An overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable.
p. Only collect fasting lipids and glucose if the Withdrawal visit occurs at Week 24, Week 48, Week 96 or Week 144.
q. A morning specimen is preferred. To assess renal biomarkers: urine albumin/creatinine ratio; urine protein/creatinine ratio; and urine phosphate.
r. 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.
s. HBV DNA testing will be performed for subjects with positive anti-HBc and negative HBsAg and negative anti-HBs (past and/or current evidence). Subjects will have to return to the clinic to provide a sample for HBV DNA testing prior to randomisation.
t. Blood samples for renal and bone biomarker assessments: **Renal:** Cystatin C; Beta-2 Microglobulin; Retinol Binding Protein (RBP); **Bone:** bone specific alkaline phosphatase, procollagen type I N-terminal propeptide, type I collagen cross-linked C-telopeptide, osteocalcin, 25-hydroxyvitamin D. Urine sample for renal biomarker assessments: RBP and Beta-2-Microglobulin. Only collect at the Withdrawal visit if it occurs at Week 24, Week 48, Week 96 or Week 144.
u. Whole blood samples may be used for virologic analyses as described in the protocol; a sample at Day 1 and a second sample at either Week 148 or at Withdrawal (if a subject is withdrawn prior to Week 148) will be taken for all subjects. Additionally, where possible, stored whole blood from Day 1 will be used for telomere length evaluation (while telomere length evaluation at Week 96 and Week 144 require a separate whole blood sample).
v. Whole blood samples for telomere length evaluation will be taken at Week 96 and Week 144 (where possible, the Day 1 evaluation will be done from the stored whole blood 'virology/telomere length' sample in footnote 'u').
w. At Screening, a subject number will be generated.

7.2. Screening and Critical Baseline Assessments

Written informed consent must be obtained from each potentially eligible subject (or his/her legal representative) by study site personnel prior to the initiation of any Screening procedures as outlined in this protocol. The consent form must have been approved by the IRB/Independent Ethics Committee (IEC). After signing an informed consent, subjects will complete Screening assessments to determine subject eligibility. Each subject being screened for study enrolment evaluation will be assigned a subject number at the Screening visit. This number will be given sequentially in chronological order of subject presentation according to a numeric roster provided by GSK/PPD.

7.2.1. Screening Assessments

Assessments to be conducted at Screening are provided in the Time and Events Table (Section 7.1).

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.

Cardiovascular medical history/risk factors (as detailed in the CRF) will be assessed at screening and assessments will include height, weight, blood pressure, smoking status and history, pertinent medical conditions (e.g. hypertension, diabetes mellitus), and family history of premature cardiovascular disease.

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.

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 subjects must provide a plasma sample for determination of viral genotypic resistance at 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 [IAS-USA, 2014]. The study virologists will confirm the lack or presence of exclusionary resistance mutations, and communicate eligibility based on the resistance test results.

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 subjects with a CrCL <50 mL/min per 1.73 m^2 are excluded due to requirements for dose reduction of 3TC or dose interval adjustments of TDF/FTC in patients with renal dysfunction.

Subjects 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 randomisation for subjects with positive anti-HBc and both negative HBsAg and anti-HBs (past and/or current evidence).

All subjects will be screened for syphilis using a rapid plasma reagin (RPR) at Screening. Subjects with untreated syphilis infection, defined as a positive RPR without clear documentation of treatment, are excluded. Subjects with a positive RPR test who have not been treated may be rescreened at least 14 days after completion of antibiotic treatment for syphilis.

Subjects who meet all entry criteria may be randomly assigned as soon as all Screening assessments are complete and the results are available and documented. All subjects will complete the Screening period of approximately 28 days (extendable to 35 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 randomisation.

Subjects not meeting all inclusion and exclusion criteria at initial screen may be rescreened and receive a new subject number one time unless they were excluded for reason of having exclusionary historic genotypic resistance. Subjects who are randomised into the trial and subsequently withdrawn from the study for any reason may not be rescreened.

7.2.2. Baseline Assessments

Assessments to be conducted at Baseline (Day1) are provided in the Time and Events Table (Section 7.1).

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

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

7.3. Efficacy

Plasma HIV-1 RNA

Plasma for quantitative HIV-1 RNA will be collected according to the Time and Events Table (Section 7.1). 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 characterise 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 Time and Events Table (Section 7.1).

CDC HIV-1 Classification and HIV Associated Conditions

HIV-associated conditions will be recorded as per the Time and Events Table (Section 7.1). HIV associated conditions will be assessed according to the 2014 CDC Classification System for HIV Infection in Adults (see Appendix 5, Section 12.5). Indicators of clinical disease progression are defined as:

CDC Stage 1 at enrolment → Stage 3 event;

CDC Stage 2 at enrolment → Stage 3 event;

CDC Stage 3 at enrolment → New Stage 3 Event;

CDC Stage 1, 2 or 3 at enrolment → Death.

7.4. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1).

7.4.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

The definitions of an AE or SAE can be found in Appendix 7, Section 12.7.

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.4.1.1. Time period and Frequency for collecting AE and SAE information

- Any SAEs assessed as related to study participation (e.g. protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a ViiV Healthcare/GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- AEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.4.1.3), at the time points specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- All SAEs will be recorded and reported to the Medical Monitor within 24 hours, as indicated in Appendix 7, Section 12.7.7.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any

time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify the Medical Monitor.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to ViiV Healthcare/GSK/PPD are provided in Appendix 7, Section 12.7.

7.4.1.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

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

7.4.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, until the condition stabilises, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 7, Section 12.7.

7.4.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 7 (Section 12.7.3) and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs 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 CRF 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.

7.4.1.5. 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 5, Section 12.5) 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/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 12.7.2), or
- The event or outcome is in the investigator's opinion of greater intensity, frequency or duration than expected for the individual subject, 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.

7.4.1.6. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to ViiV Healthcare or designee of SAEs related to study treatment is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product 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 product under clinical investigation. ViiV Healthcare/GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/ IEC and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and ViiV Healthcare/GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE(s) or other specific safety information (e.g. summary or listing of SAEs) from ViiV Healthcare/GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

7.4.2. Pregnancy

- Details of all pregnancies in female subjects will be collected after the start of dosing and until and ending at the final Follow-up visit.
- If a pregnancy is reported then the investigator should inform ViiV Healthcare/GSK/PPD within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 9, Section 12.9.2.

7.4.3. Physical Exams

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

7.4.4. Electrocardiogram (ECG)

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).

7.4.5. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Section 7.1, must be performed by the central laboratory, Q^2 Solutions, or a laboratory contracted by the central laboratory. Laboratory assessments must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by Q^2 Solutions and are detailed in the laboratory manual. Reference ranges for all safety parameters will be provided to the site by Q^2 Solutions.

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

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

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

Table 1 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Haematology	Platelet Count; RBC Count; WBC Count (absolute); Haemoglobin; Haematocrit *RBC Indices*: MCV; MCH *Automated WBC Differential:* Neutrophils; Lymphocytes; Monocytes; Eosinophils; Basophils
Clinical Chemistry [1]	BUN; Chloride; Alkaline phosphatise; Creatine phosphokinase Creatinine; Calcium; Phosphate; Creatinine clearance [4] Glucose [2]; Total CO_2; Total bilirubin [3]; Lipase Potassium; AST; Total protein Sodium; ALT; Albumin
Fasting Lipid Panel [5]	• Total cholesterol • HDL cholesterol • LDL cholesterol • Triglycerides
Other Laboratory Tests	• Plasma HIV-1 RNA [6] • CD4+ cell counts • Hepatitis B (HBsAg, anti-HBc, anti-HBs, HBV DNA) • Hepatitis C (anti-HCV) • RPR • PT/INR • Serum hCG pregnancy test (as needed for females of reproductive potential) [7] • Urinalysis, urine albumin/creatinine ratio, and urine protein/creatinine ratio, urine phosphate • Renal biomarkers including Cystatin C (blood), Retinol Binding Protein (RBP, blood/urine); and Beta-2 Microglobulin (B2M, blood/urine) [8] • Bone biomarkers including: bone-specific alkaline phosphatase, procollagen type I N-terminal propeptide, type I collagen cross-linked C-telopeptide, osteocalcin, 25-hydroxyvitamin D [8] • Inflammation biomarkers including IL-6 and hs-CRP [8] • Telomere length [8]

ALT = alanine aminotransferase, anti-HBc = hepatitis B core antibody, anti-HBs = hepatitis B surface antibody, anti-HCV = hepatitis C antibody, AST = aspartate aminotransferase, BUN = blood urea nitrogen, CO_2 = carbon dioxide, HBsAg = hepatitis B surface antigen, HBV DNA = hepatitis B virus deoxyribonucleic acid, HDL = high density lipoprotein, LDL = low density lipoprotein, MCH = mean corpuscular haemoglobin, MCV = mean corpuscular volume, PT/INR = prothrombin time/international normalised ratio, RBC = red blood cells, RPR = rapid plasma reagin, WBC = white blood cells, IL-6 = interleukin 6, hs-CRP = high-sensitivity C-reactive protein

NOTES :

1. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-up Assessments after liver stopping or monitoring event are given in Section 5.4.2 and Appendix 3, Section 12.3. Details of other stopping/withdrawal criteria and Toxicity Management are given in Section 5.4 and Appendix 8, Section 12.8.
2. For fasting glucose assessments, an overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable for subjects with afternoon appointments.
3. Direct bilirubin will be reflexively performed for all total bilirubin values >1.5× ULN.
4. Glomerular filtration rate (GFR) will be estimated by the central laboratory using the CKD-EPI method [Levey, 2009].
5. For fasting lipids assessments, an overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable for subjects with afternoon appointments.
6. For subjects meeting virologic withdrawal criteria, plasma samples will be analysed in attempt to obtain genotype/phenotype data.
7. Pregnancy testing will be conducted on serum samples with the exception of Day 1, when a urine test is used to confirm status prior to administration of study treatment.
8. Since the intention is to utilise these biomarker data for research purposes, the sponsor will not be reporting the results of these assessments to the investigator, except for some individual renal biomarkers and 25-hydroxyvitamin D. No summary analysis of biomarker data will be made until a study endpoint is reached.

All laboratory tests with values that are 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. If such values do not return to normal within a period judged reasonable by the investigator, the aetiology should be identified and the sponsor notified.

7.4.6. Suicidal Risk Monitoring

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

Subjects should be monitored appropriately and observed closely for suicidal ideation and behaviour or any other unusual changes in behaviour. It is recommended that the investigator consider mental health consultation or referral for subjects who experience signs of suicidal ideation or behaviour. Subjects 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.

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 behavioural suicidal events used in this scale are based on those used in the Columbia Suicide History Form [Posner, 2007]. Questions are asked on suicidal behaviour, 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) and all subsequent questioning in relation to the last assessment. The eC-SSRS is to be administered as a patient completed questionnaire specified in the Time and Events Table (Section 7.1). 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 subject 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 behaviour, 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/PPD within 1 week of the investigator diagnosing a possible suicidality-related AE.

7.5. Biomarkers

Blood and/or urine are being collected to perform evaluations of renal, bone and inflammation biomarkers, and telomere length as outlined in Section 7.1.

Renal biomarkers include:
- Cystatin C (blood)
- Retinol Binding Protein (RBP, blood/urine),
- Beta-2-Microglobulin (B2M, blood/urine),
- urine albumin/creatinine ratio,
- urine protein/creatinine ratio,
- urine phosphate, and
- serum creatinine.

Bone biomarkers (blood) include:
- bone-specific alkaline phosphatase,
- procollagen type 1 N-propeptide,
- type 1 collagen cross-linked C-telopeptide,
- osteocalcin, and
- 25-hydroxyvitamin D.

Inflammation biomarkers include:
- interleukin-6 (IL-6, blood)
- high-sensitivity C reactive protein (hs-CRP, blood)

Telomere length (whole blood)

Since the intention is to utilise these biomarkers for research purposes, the Sponsor will not be reporting the results of these assessments to the investigator except for some renal

biomarkers and 25-hydroxyvitamin D. No summary analysis of biomarker data will be made until a study endpoint is reached.

7.6. HIV-1 Polymerase Viral Genotyping and Phenotyping

Whole venous blood samples will be obtained from each subject to provide plasma for storage samples according to the Time and Events Table (Section 7.1). Subjects meeting CVW criteria will have plasma samples tested for HIV-1 PRO and RT genotype and phenotype and HIV-1 integrase genotype and phenotype from Baseline samples and from samples collected at the time of meeting SVW criteria; these results will be reported to the investigator as soon as available to provide guidance for election of an alternative regimen. See Section 5.4.1.3 for details.

Details concerning the handling, labelling and shipping of these samples will be supplied separately. Genotypic analyses for RT and PRO will be carried out at Screen by Q^2 Solutions, and genotypic and phenotypic analyses may be carried out by Monogram Biosciences using, but not limited to, their Standard PhenoSense and GenoSure testing methods for PRO, RT, and integrase.

7.6.1. HIV-1 Exploratory Analyses

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

Additional virologic analyses for HIV-1 may, for example, be carried out on whole blood samples collected at Baseline or on study per Time and Events Table (Section 7.1), 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 PRO and RT genotype and phenotype and HIV-1 integrase genotype and phenotype will also be determined on the last on-treatment isolates from subjects who at that time point (e.g. Withdrawal visit) have HIV-1 RNA ≥400 c/mL while receiving study treatment regardless of confirmatory HIV-1 RNA.

7.7. Value Evidence and Outcomes

The Health outcomes assessment will be conducted according to the Time and Events Table (Section 7.1). The assessment is recommended to be administered at the beginning of the visit prior to collection of blood for analysis and other scheduled assessments. The questionnaire will be administered on paper.

The European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L), developed by EuroQol group, is a standardised, generic questionnaire that provides a profile of patient function and a global health state rating. The five-item measure has one question assessing each of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression and 5 levels for each dimension including no problems, slight

problems, moderate problems, severe problems and extreme problems. The EQ-5D-5L also includes a visual analogue scale (VAS) that assesses overall health [Herdman, 2011].

7.7.1. Value Evidence and Outcomes Endpoints

- Summary statistics as well as between and within group change from Baseline in health related quality of life using EQ-5D-5L at Weeks 4, 24, 48, 96, and 144 (or Withdrawal from the study).

8. DATA MANAGEMENT

- For this study, subject data will be entered into GSK-defined CRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable PPD standards and data cleaning procedures to ensure the integrity of the data, e.g. removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA and an internal validated medication dictionary, GSKDrug.
- eCRFs (including queries and audit trails) will be retained by GSK, and copies will be sent at the end of the study in CD format to GSK to be retained. Each investigator will receive a copy of his or her site-specific data in the same format to maintain as the investigator copy. Subject initials will not be collected or transmitted to ViiV Healthcare/GSK according to ViiV Healthcare/GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

This study is designed to show that the antiviral effect of a simplified two-drug regimen of DTG plus 3TC once-daily is not inferior to a standard three-drug regimen of DTG plus TDF/FTC FDC once daily in HIV-1 infected ART-naïve adult subjects.

Non-inferiority can be concluded if the lower bound of a two-sided 95% confidence interval for the difference in response rates between the two treatment arms is greater than -10%. If r_d is the response rate on DTG plus 3TC and r_f is the response rate on DTG plus TDF/FTC FDC, then the hypotheses can be written as follows:

$$H_0: r_d - r_f \leq -10\% \qquad H_1: r_d - r_f > -10\%$$

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

Assuming a true response rate of 87% for the DTG plus 3TC arm and an 89% response rate for the DTG plus TDF/FTC arm, the study requires 347 subjects per arm to have 90% power with a 10% non-inferiority margin and a 2.5% one-sided alpha level.

9.2.1.1. Rationale for non-inferiority margin

The use of a 10% non-inferiority margin for treatment-naïve subjects is in accordance with current FDA guidance [CDER, 2015].

9.2.1.2. Response rate assumptions

Response rates at week 48 in previous studies with DTG plus two NRTIs range from 85% - 90% (Table 2). The response rate on the DTG plus TDF/FTC arm is assumed to be 89% at Week 48 based on the combined evidence. Response rates at Week 48 in previous two-drug regimen studies range from 83% - 88% (Table 2). However, there is no previous two-drug regimen study conducted with DTG. The response rate on the DTG plus 3TC arm at week 48 is assumed to be 87% combining evidence from both previous DTG studies and studies with other two-drug regimen.

Table 2 Response rates in previous DTG and two-drug regimen studies

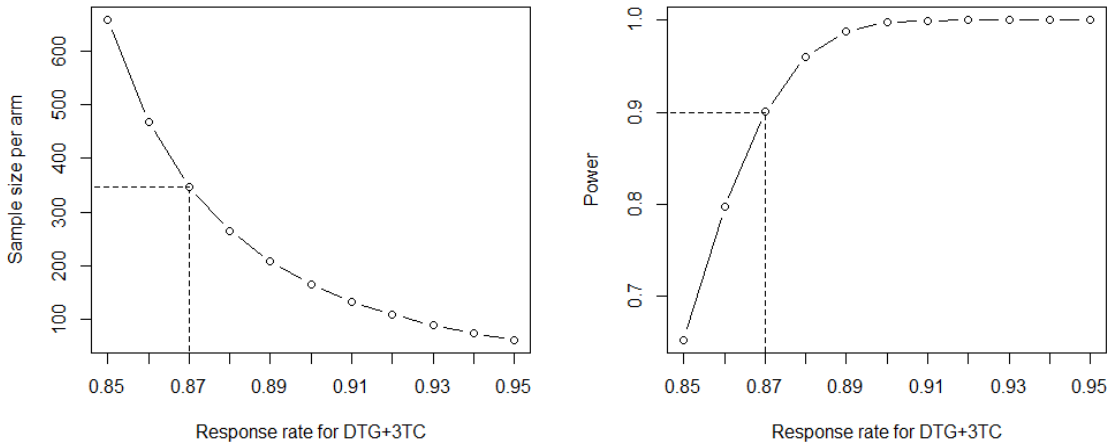
	n	Treatment regimen	Week 48 response rate (<50 c/mL)
SPRING-2[1]	411	DTG + 2 NRTIs (ABC/3TC or TDF/FTC)	88%
SINGLE[2]	414	DTG + ABC/3TC	88%
FLAMINGO[3]	242	DTG + 2 NRTIs (ABC/3TC or TDF/FTC)	90%
ACTG A5142[4]	250	LPV/RTV + EFV	83%
PROGRESS[5]	101	LPV/RTV+ RAL	83%
GARDEL[6]	214	LPV/RTV + 3TC	88%

[1] [Raffi, 2013]
[2] [Walmsley, 2013]
[3] [Clotet, 2014]
[4] [Riddler, 2008]; Week 96 response rates are shown.
[5] [Reynes, 2011]
[6] [Cahn, 2014]

9.2.2. Sample Size Sensitivity

Figure 2 shows sensitivity of the required sample size to the true response rate for the DTG plus 3TC arm assuming an 89% response rate in the DTG plus TDF/FTC arm.

Figure 2 Sample Size Sensitivity



9.2.3. Sample Size Re-estimation or Adjustment

No sample size re-estimation will be performed.

9.3. Data Analysis Considerations

The following populations will be assessed. The analysis population for genotypic and phenotypic analyses will be fully described in the reporting and analysis plan (RAP).

9.3.1. Analysis Populations

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

This population will consist of all randomised subjects who receive at least one dose of study medication. Subjects will be assessed according to their randomised treatment, regardless of the treatment they receive. Unless stated otherwise, the ITT-E Population will be used for efficacy analyses.

9.3.1.2. Per Protocol (PP) Population

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

9.3.1.3. Safety Population

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

9.3.2. Analysis Data Sets

Subjects' responses at <50 c/mL will be calculated according to a Missing, Switch or Discontinuation = Failure (MSD=F) algorithm – as codified by the FDA's snapshot algorithm. This algorithm treats all subjects 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 subjects who switch their concomitant ART prior to the visit of interest since no switches are allowed in this protocol.

Otherwise, virologic success or failure will be determined by the last available HIV-1 RNA assessment while the subject is on-treatment within the visit of interest window (as specified in the RAP).

Full details of this snapshot algorithm will be contained in the RAP.

A secondary set of data will treat subjects 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 will be the primary dataset for assessing safety.

9.3.3. Treatment Comparisons

9.3.3.1. Primary Comparison of Interest

The primary analysis will be based on the ITT-E population using the Snapshot dataset. The primary comparison will be made at a one-sided 2.5% level of significance. Treatment with DTG plus 3TC will be declared non-inferior to treatment with DTG plus TDF/FTC FDC if the lower end of a two-sided 95% confidence interval for the difference between the two groups in response rates at Week 48 lies above -10%.

9.3.3.2. Other Comparisons of Interest

The analysis described above will also be performed using the PP population and the results will be compared for consistency with the results from the ITT-E population. If both analyses show non-inferiority then the hypothesis that the antiviral effect of treatment with DTG plus 3TC is superior to treatment with DTG plus TDF/FTC FDC will be tested using the same level of significance as for the tests of non-inferiority. Superiority will be declared if the lower end of the confidence internal is above 0%. The primary comparison will also be performed using the ITT population and will be compared for consistency with the results from the ITT-E and PP populations.

9.3.3.3. Secondary comparisons

The following key secondary comparison will be tested:

- Superiority of DTG plus 3TC compared to DTG plus TDF/FTC FDC with respect to change from baseline in CD4+ cell counts;

- Superiority of DTG plus 3TC compared to DTG plus TDF/FTC FDC with respect to renal biomarkers, RBP and B2M.

No multiplicity adjustments for statistical testing of secondary endpoints will be performed; however, all tests will be pre-specified in the RAP.

9.3.4. Interim Analyses

At least four analyses will be conducted to evaluate primary and secondary objectives of the protocol, one when all subjects have completed their visits at Week 24, at Week 48, at Week 96, and at Week 144. Further data cuts and analyses may be conducted as necessary after Week 144 in order 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 24, Week 96 and Week 144 analyses will be secondary. ViiV Healthcare/GSK/PPD will unblind the study for the purpose of the Week 24 analysis; however, subjects and investigators will remain blinded to treatment allocation until each subject has reached their Week 96 visit. The Week 24 analysis will be used for regulatory purposes and no external presentation of the data will occur until at least all patients have reached the Week 48 visit (when the primary analysis will occur).

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 and sister study 205543. 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. Further, an interim futility analysis will be performed for the IDMC to evaluate the efficacy and safety of DTG plus 3TC when approximately 50% of subjects have completed their visit at Week 24; the sponsor will remain blinded to this analysis. Full details of the methods, timing, decision criteria and operating characteristics will be pre-specified in the IDMC Charter.

9.4. Key Elements of Analysis Plan

9.4.1. Efficacy Analyses

For the primary comparison, adjusted estimates of the difference in the rate of responders between the two arms will be presented along with CIs based on a stratified analysis using Cochran-Mantel-Haenszel (CMH) weights. All CIs will be two-sided. For the statistical analysis, four strata (subgroups) will be formed according to the combinations of levels of the following categorical variables:

- Baseline plasma HIV-1 RNA (≤ vs.>100,000c/mL);
- Baseline CD4+ cell count (≤ vs. >200 cells/mm^3).

The CMH estimate of the common difference in rates across strata will be calculated as the weighted average of the strata-specific estimates of the difference in response rates between the two arms as follows.

If n_k is the number of DTG plus 3TC treated subjects, m_k is the number of DTG plus TDF/FTC treated subjects, and $N_k = n_k + m_k$ is the total number of subjects in the k^{th} stratum, then the CMH estimate is given by

$$\hat{d}_{cmh} = \frac{\sum W_k \hat{d}_k}{\sum W_k}$$

where

$$W_k = \frac{n_k m_k}{N_k}$$

are CMH weights and $\hat{d}_k$ are estimates of the differences in response rates between the two treatment arms, $r_d - r_f$, for the k^{th} strata.

The corresponding two-sided 95% CI will be calculated as

$$\hat{d}_{cmh} \pm 1.96 \times \sqrt{\widehat{var}(\hat{d}_{cmh})}$$

using the variance estimator $\widehat{var}(\hat{d}_{cmh})$ given by [Sato, 1989] which is consistent in both sparse data and large strata. The full equation for this variance estimate is provided in the RAP. Full details will be contained in the RAP.

The weighted least squares chi-squared statistic [Fleiss, 1981] will be used to test for one-way homogeneity across the levels of each categorical variable, with each categorical variable considered separately. Following Lui and Kelly [Lui, 2000], ½ will be added to each cell in any strata for which the stratum-specific rate estimates of either r_d or r_f are zero, and tests will be one-sided. Any heterogeneity found to be statistically significant will be explored and if necessary results will be reported for each level of the categorical variable. Investigation of heterogeneity will be confined to the primary endpoint using the Week 24 and Week 48 Snapshot analyses. Tests of homogeneity will be assessed at the one-sided 10% level of significance.

A sensitivity analysis will be performed at Week 48 to assess whether bias was introduced by the unblinded analysis performed at Week 24. The Week 48 Snapshot results of the subjects who reached Week 48 prior to the Week 24 unblinding will be compared to the Week 48 results in the subjects who reached Week 48 after the Week 24 unblinding.

Further efficacy analyses to assess the sensitivity of the primary endpoint will be performed. Details of the sensitivity analyses will be included in the RAP and will include 'time to event' methods which censor subjects who discontinue from the study with viral load <50 c/ml or for non-efficacy-treatment related reasons. In these analyses, subjects will be considered to have had an event if they have a confirmed viral load ≥50 c/ml or discontinue for efficacy-related reasons.

The incidence of HIV-1 disease progression (AIDS and death) will be presented. The proportion of subjects with plasma HIV-1 RNA <50 c/mL and changes from baseline in CD4+ cell count will be summarised by subgroups (e.g. age, gender, race, baseline CD4+ cell counts).

Details for secondary efficacy endpoints will be discussed in the RAP.

Data gathered after subjects withdraw from study treatment will be listed but will not be included in summary tables. Data will be allocated to visit windows using actual visit dates rather than nominal visit numbers. Data collected from extra visits within a window will be listed and will be included in the derivation of the Snapshot response at analysis visits of interest, but summary tables using OC datasets will only use the data captured closest to the target visit date. Detailed explanations of the derivation of visit windows will be included in the RAP. Any deviations from planned analyses will be detailed in the clinical study report (CSR).

9.4.2. Safety Analyses

The observed case dataset will be the primary dataset used for analysis of safety endpoints.

Exposure to study medication, measured by the number of weeks on study drug, will be summarised by treatment group. The proportion of subjects reporting AEs will be tabulated for each treatment group. 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; and
- Incidence of SAEs.

Statistical analysis of selected biomarkers and fasting lipids may be performed overall and by baseline demographics using appropriate methods for missing data. Further details will be provided in the RAP.

Laboratory, biomarker and vital signs data will be summarised by visit and treatment group. In addition, the number and percentage of subjects with graded laboratory toxicities (based on DAIDS categories; Appendix 6, Section 12.6) will be summarised by treatment group. The proportion of subjects experiencing changes from Baseline in their National Cholesterol Education Program (NCEP) lipid categories will be summarised by treatment arm. Further details of safety analyses will be included in the RAP.

9.4.3. Viral Genotyping/Phenotyping Analyses

The incidence of treatment-emergent genotypic and phenotypic resistance to DTG, 3TC and TDF/FTC will be summarised by treatment arm for subjects meeting CVW criteria (Section 5.4.1). Details of the analyses to be performed will be specified in the RAP.

9.4.4. Other Analyses

The change from Baseline in health related quality of life using EQ-5D-5L will be summarised as detailed in Section 7.7.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. 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 subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a site, ViiV Healthcare/GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements, and with ViiV Healthcare/GSK policy.

The study will also be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable;
- Obtaining signed informed consent;
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC).

ViiV Healthcare/GSK/PPD will provide full details of the above procedures, either verbally, in writing, or both.

Signed informed consent must be obtained for each subject (or his/her legal representative) prior to participation in the study (and for amendments as applicable).

10.3. Quality Control (Study Monitoring)

- 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 subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents

10.4. Quality Assurance

- 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.

10.5. 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 temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicentre studies, this can occur at one or more or at all sites.
- If ViiV Healthcare/GSK determines such action is needed, ViiV Healthcare/GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, ViiV Healthcare/GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, ViiV Healthcare/GSK/PPD will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. ViiV Healthcare/GSK/PPD will also promptly inform the relevant regulatory authorities of

the suspension or premature discontinuation of the study and the reason(s) for the action.

- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. 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.
- The Investigator's Site Files must be retained for 25 years from the date of the final CSR. ViiV Healthcare, GSK or PPD will inform the investigator of the retention period due date at the time when this CSR (or equivalent) is issued to the site.
- 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.

10.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

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 subjects, as appropriate.

ViiV Healthcare/GSK will provide the investigators with the randomisation codes for their sites only after completion of the full statistical analysis.

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.

10.8. Independent Data Monitoring Committee

An IDMC will be utilised 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 subjects and to protect the scientific validity of this study and sister study 205543. The schedule of any planned interim analysis and the analysis plan for IDMC review is described in the 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.

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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
B2M	Beta-2 Microglobulin
BMI	Body mass index
c/mL	Copies/millilitre
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMH	Cochran-Mantel-Haenszel
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CrCl	Creatinine clearance
CRF	Case report form
CSR	Clinical study report
C-SSRS	Columbia Suicidality Severity Rating Scale
CV	Cardiovascular
CVW	Confirmed Virologic Withdrawal
DAIDS	Division of Acquired Immunodeficiency Syndrome
DILI	Drug induced liver injury
DNA	Deoxyribonucleic acid
DRV	Darunavir
DTG	Dolutegravir, TIVICAY
ECG	Electrocardiogram
eCRF	Electronic case report form
eC-SSRS	Electronic Columbia Suicidality Severity Rating Scale
EFV	Efavirenz
EQ-5D-5L	EuroQol – 5 Dimensions – 5 Levels
EU	European Union
FDA	Food and Drug Administration
FDC	Fixed-dose combination
FRP	Females of Reproductive Potential
FSH	Follicle stimulating hormone
FTC	Emtricitabine

GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GFR	Glomerular filtration rate
GSK	GlaxoSmithKline
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	Human chorionic gonadotrophin
HCV	Hepatitis C virus
HDL	High density lipoprotein
HDPE	High density polyethylene
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HPMC	Hydroxypropyl methylcellulose
HRT	Hormone replacement therapy
hs-CRP	High-sensitivity C-reactive protein
HSR	Hypersensitivity reaction
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
IL-6	Interleukin-6
INR	International normalised ratio
INSTI	Integrase strand transfer inhibitor
IP	Investigational Product
IRB	Institutional Review Board
ITT-E	Intent-to-treat exposed
IVRS	Interactive voice recognition system
IWRS	Interactive web recognition system
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LPV	Lopinavir
MCH	Mean corpuscular haemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
mg	Milligram
mg/dL	Milligram per decilitre
MSD=F	Missing, switch, or discontinuation equals failure
MSDS	Material Safety Data Sheet
NCEP	National Cholesterol Education Program
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
OC	Observed case
OCT2	Organic cation transporter 2
PBMC	Peripheral blood mononuclear cell
PEP	Post-exposure prophylaxis
PI	Protease inhibitor

PK	Pharmacokinetic(s)
PP	Per-protocol
PPD	Pharmaceutical Product Development
PrEP	Pre-exposure prophylaxis
PRO	Protease
PRTD	Proximal Renal Tubule Dysfunction
PSRAE	Possible suicidality-related adverse event
RAL	Raltegravir
RAP	Reporting and Analysis Plan
RBC	Red blood cell
RBP	Retinol Binding Protein
RNA	Ribonucleic acid
RPR	Rapid plasma reagin
RT	Reverse transcriptase
RTV	Ritonavir
SAE	Serious adverse event
SJS	Stevens-Johnson syndrome
SRM	Study Reference Manual
STR	Single tablet regimen
SVW	Suspected Virologic Withdrawal
TDF	Tenofovir disoproxil fumarate
TEN	Toxic epidermal necrolysis
TRDF	Treatment Related Discontinuation = Failure
ULN	Upper limit of normal
US	United States
VAS	Visual analogue scale
VSLC	ViiV Healthcare Safety and Labelling Committee
WBC	White blood cell
ZDV	Zidovudine, RETROVIR
ZDV/3TC	Zidovudine/lamivudine, COMBIVIR

Trademark Information

Trademarks of ViiV Healthcare
COMBIVIR
EPIVIR
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TIVICAY
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Trademarks not owned by ViiV Healthcare
Abbott RealTime
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Monogram Biosciences
PhenoSense
Q^2 Solutions
Truvada

12.2. Appendix 2: Child-Pugh Classification

A subject is classified with mild hepatic impairment (Class A) if their overall sum of scores is 5-6 points, moderate hepatic impairment (Class B) if their overall sum of scores is 7-9 points, and severe hepatic impairment (Class C) if their overall sum of scores is 10-15 based on the Child-Pugh system [Pugh, 1973] scoring described in the following table (Table 3). For subjects requiring anticoagulation therapy, discussion with the study Medical Monitor will be required.

Table 3 Child-Pugh System

Finding	Points Scored for Each Observed Finding		
	1	2	3
Encephalopathy Grade[1]	None	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Serum bilirubin, SI units (µmol/L), Serum bilirubin, conventional units (mg/dL)	<34 <2	34 to 52 2 to 3	>52 >3
Serum albumin, SI units (g/L) Serum albumin, conventional units (mg/dL)	>35 >3.5	28 to 35 2.8 to 3.5	<28 <2.8
Prothrombin Time (seconds prolonged) or INR	<4 <1.7	4 to 6 1.7 to 2.3	>6 >2.3

1. Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles per second waves
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4: unrousable coma, no personality/behaviour, decerebrate, slow 2-3 cycles per second delta activity
[Pugh, 1973; Lucey, 1997]

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

Liver Chemistry Stopping Criteria - Liver Stopping Event	
ALT-absolute	ALT ≥ 8xULN
ALT Increase	ALT ≥ 5xULN but <8xULN persists for ≥2 weeks (with bilirubin <2xULN and no signs or symptoms of acute hepatitis or hypersensitivity)
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
Cannot Monitor	ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for >2 weeks
Symptomatic[3]	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

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**

• Immediately discontinue study treatment.
• Report the event to the Medical Monitor **within 24 hours**.
• Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2].
• Complete the liver imaging and/or liver biopsy eCRFs if these tests are performed.
• Perform liver event follow up assessments.
• Monitor the subject until liver chemistries resolve, stabilise, or return to within baseline (see **MONITORING** below).
• **Do not restart** subject with study treatment unless allowed per protocol and VSLC approval **is granted** (refer to Appendix 4).
• If restart is **not allowed or not granted**, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments.
	Make every attempt to carry out liver event follow-up assessments at the central laboratory as described below:
	• 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.
	• Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen

MONITORING: • Make every reasonable attempt to have subjects return to clinic within **24 hours** for repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments. • Monitor subjects twice weekly until liver chemistries resolve, stabilise or return to within baseline. • A specialist or hepatology consultation is recommended.	contribution to liver injury in subjects 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 computerised 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. • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake CRF.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject 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 subjects 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 CRF. If the date or time of the last dose is unclear, provide the subject'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 SRM.

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 subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until resolution or stabilisation (ALT <5×ULN on 2 consecutive evaluations) • If at any time subject meets the liver chemistry stopping criteria, proceed as described above

Reference

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

12.4. Appendix 4: Liver Safety – Study Treatment Restart Guidelines

VSLC GUIDELINES FOR DRUG RESTART AFTER STOPPING FOR LIVER CRITERIA

In Phase III, **drug restart** may be considered for liver events with a clear underlying cause (e.g., biliary, pancreatic events, hypotension, acute viral hepatitis), if not associated with drug-induced liver injury, alcoholic hepatitis or hypersensitivity, and drug not associated with human leukocyte antigen (HLA) marker of liver injury, when liver chemistries improve to within 1.5x baseline and ALT<3xULN) (Table 4, Figure 3).

Drug Restart

Phase III "drug restart" can be approved by the VSLC for **transient, defined non-drug-induced liver injury if no evidence of:**

- immunoallergic injury /HLA association with injury
- drug-induced liver injury (DILI)
- alcoholic hepatitis

Study drug is held while labs and evaluation is completed to assess diagnosis.

VSLC Decision Process for Drug Restart Approval or Disapproval (Figure 3):

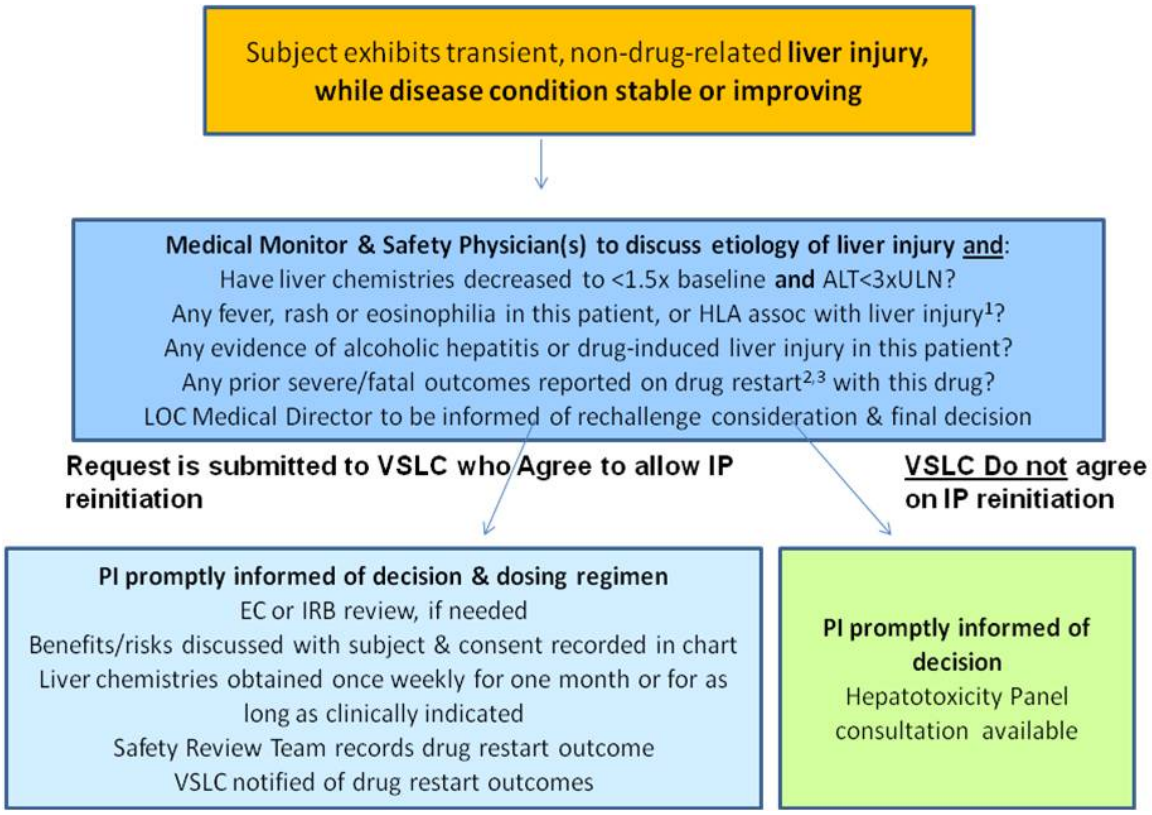
- PI requests consideration of drug re-initiation for a subject stable or improving on study drug, who exhibits liver chemistry elevation meeting subject stopping criteria, which is transient, non-drug-related, and liver chemistries improve to within 1.5x baseline and ALT< 3xULN.
- Medical monitor and Clinical Safety Physician to review the subject's diagnosis, restart risk factors and complete checklist (Table 4).
  - The LOC medical director (ViiV Healthcare and GSK where applicable) should be informed that study drug restart is under consideration and of the final decision, whether or not to proceed.

Table 4 Checklist for Phase III drug restart after well-explained liver injury (e.g., biliary, pancreatic, hypotensive events, congestive heart failure, acute viral hepatitis), improving to liver chem.≤1.5x baseline & ALT<3xULN

	Yes	No
Was subject stable or improving on study drug?		
Do not restart if the **following risk factors at initial liver injury**:		
• fever, rash, eosinophilia, or hypersensitivity		
• drug-induced liver injury		
• alcoholic hepatitis (AST>ALT, typically <10xULN)		
• study drug has an HLA genetic marker associated with liver injury (e.g., lapatinib, abacavir, amoxicillin/clavulanate)		
Previous drug history		

- Relevant physicians must review and agree on request for drug restart:
  - Safety Team Leader, VP, or Senior Safety Physician
  - Medicines Development Leader and Project Physician Leader.
- Hepatotoxicity Panel consultation is available.
- Justification for drug restart outlining the benefit and risk for this subject must be recorded by GCSP Physician and sent to the VSLC Secretary.
  - VSLC must approve drug re-initiation and dosing regimen

Figure 3 VSLC process for drug restart approval or disapproval



1. Andrade, 2009; 2. Papay, 2009; 3. Hunt, 2010

Medical Monitor, GCSP Physician and PI actions for Restart following VSLC decision

Medical Monitor and (Global Clinical Safety and Pharmacovigilance) GCSP Physician Actions

- Medical Monitor must notify PI of VSLC's restart decision and recommended dosing regimen in writing and Medical Monitor must record note in study files.
- The Safety Review Team must record restart outcomes and the GCSP Physician must send these to the VSLC
  - All severe reactions (restart associated with bilirubin>2xULN or jaundice, or INR≥1.5), SAEs or fatalities with drug restart must be immediately reported to Line Management, VSLC Chair, VP Global Medical Strategy and EU Qualified Person for Pharmacovigilance.

Principal Investigator Actions:

- The PI must obtain Ethics Committee or Institutional Review Board approval of drug restart, as required.
- If drug re-initiation VSLC-approved, the patient must provide informed consent with a clear description of possible benefits and risks of drug administration including recurrent, more severe liver injury or possible death.
- The patient's informed consent must be recorded in the study chart, and the drug administered at agreed dose, as communicated by Medical Monitor.
- Liver chemistries must be followed ***once weekly for 'restart' cases*** for one month or for as long as clinically indicated following drug re-initiation. If subject exhibits protocol-defined liver chemistry elevations, study drug should be discontinued as protocol specified.

VSLC and the IRB/IEC must be informed of the patient's outcome following drug restart.

Restart safety outcomes:

- 0 = no liver chemistry elevation
- 1 = recurrent liver chemistry elevation not meeting subject stopping criteria
- 2 = recurrent liver chemistry elevation meeting subject stopping criteria
- 3 = serious adverse event
- 4 = fatality

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, et al. Drug-induced liver injury following positive drug rechallenge. Regul Tox Pharm. 2009; 54:84-90.

12.5. Appendix 5: CDC Classification for HIV-1 Infection (2014)

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.

Stage 3-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

CDC. Revised Surveillance Case Definition for HIV Infection – United States, 2014. MMWR 2014; 63 (RR-03);1-10.

12.6. Appendix 6: Division of AIDS table for Grading Severity of Adult and Pediatric Adverse Events

VERSION 2.0, November 2014

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 utilised for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical adverse event **NOT** identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

Major Clinical Conditions

Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arrhythmia (by ECG or physical examination) *Specify type, if applicable*	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Blood Pressure Abnormalities[1] ***Hypertension*** *(with the lowest reading taken after repeat testing during a visit)* *≥ 18 years of age*	140 to < 160 mmHg systolic OR 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
< 18 years of age	> 120/80 mmHg	≥ 95th to < 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥ 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Cardiac Ischemia or Infarction *Report only one*	NA	NA	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR Intervention indicated (e.g., oxygen)	Life-threatening consequences OR Urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)
Hemorrhage (with significant acute blood loss)	NA	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤ 2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children, packed RBCs > 10 cc/kg) indicated
Prolonged PR Interval or AV Block *Report only one* *> 16 years of age*	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
≤ 16 years of age	1st degree AV block (PR interval > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
Prolonged QTc Interval[2]	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds OR ≥ 0.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism *Report only one*	NA	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)

[1] Blood pressure norms for children < 18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. Pediatrics 2011;128;S213; originally published online November 14, 2011; DOI: 10.1542/peds.2009-2107C.
[2] As per Bazett's formula.

Dermatologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one	Generalized	NA
Pruritus[3] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis

[3] For pruritus associated with injections or infusions, see the Site Reactions to Injections and Infusions section.

Endocrine and Metabolic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma, end organ failure)
Gynecomastia	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Lipoatrophy[4]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA
Lipohypertrophy[5]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

[4] Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.
[5] Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.

Gastrointestinal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequencs
Bloating or Distension *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea *≥ 1 year of age*	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
< 1 year of age	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Life-threatening consequences (e.g., liquid stools resulting in severe dehydration, hypotensive shock)
Dysphagia or Odynophagia *Report only one and specify location*	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)
Mucositis or Stomatitis **Report only one and specify location**	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Nausea	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Perforation (colon or rectum)	NA	NA	Intervention indicated	Life-threatening consequences

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NA	NA
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

Musculoskeletal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arthralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	No symptoms but with radiographic findings AND No operative intervention indicated	Bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
Osteopenia[6] *≥ 30 years of age*	BMD t-score -2.5 to -1	NA	NA	NA
< 30 years of age	BMD z-score -2 to -1	NA	NA	NA
Osteoporosis[6] *≥ 30 years of age*	NA	BMD t-score < -2.5	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
< 30 years of age	NA	BMD z-score < -2	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences

[6] BMD t and z scores can be found in: Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.

Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute CNS Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
Altered Mental Status (for Dementia, see *Cognitive, Behavioral, or Attentional Disturbance* below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR Obtundation OR Coma
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, Behavioral, or Attentional Disturbance (includes dementia and attention deficit disorder) *Specify type, if applicable*	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part- time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full- time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Developmental Delay *< 18 years of age* *Specify type, if applicable*	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function
Neuromuscular Weakness (includes myopathy and neuropathy) **Specify type, if applicable**	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation

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

Pregnancy, Puerperium, and Perinatal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Fetal Death or Stillbirth (report using mother's participant ID) *Report only one*	NA	NA	Fetal loss occurring at ≥ 20 weeks gestation	NA
Preterm Delivery[7] (report using mother's participant ID)	Delivery at 34 to < 37 weeks gestational age	Delivery at 28 to < 34 weeks gestational age	Delivery at 24 to < 28 weeks gestational age	Delivery at < 24 weeks gestational age
Spontaneous Abortion or Miscarriage[8] (report using mother's participant ID) *Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA

[7] Definition: A delivery of a live-born neonate occurring at ≥ 20 to < 37 weeks gestational age.
[8] Definition: A clinically recognized pregnancy occurring at < 20 weeks gestational age.

Psychiatric

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early	Moderate difficulty falling asleep, staying asleep, or waking up early	Severe difficulty falling asleep, staying asleep, or waking up early	NA
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) *Specify disorder*	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions
Suicidal Ideation or Attempt *Report only one*	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated	Suicide attempted

Respiratory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥ 70 to < 80% OR Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50 to < 70% OR Symptoms with intervention indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Forced expiratory volume in 1 second or peak flow 25 to < 50% OR Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow < 25% OR Life-threatening respiratory or hemodynamic compromise OR Intubation
Dyspnea or Respiratory Distress *Report only one*	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 to < 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)

Sensory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hearing Loss *≥ 12 years of age*	NA	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (> 80 dB at 2 kHz and above) OR Non-serviceable hearing (i.e., >50 dB audiogram and <50% speech discrimination)
< 12 years of age (based on a 1, 2, 3, 4, 6 and 8 kHz audiogram)	> 20 dB hearing loss at ≤ 4 kHz	> 20 dB hearing loss at > 4 kHz	> 20 dB hearing loss at ≥ 3 kHz in one ear with additional speech language related services indicated (where available) OR Hearing loss sufficient to indicate therapeutic intervention, including hearing aids	Audiologic indication for cochlear implant and additional speech-language related services indicated (where available)
Tinnitus	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	NA
Uveitis	No symptoms AND Detectable on examination	Anterior uveitis with symptoms OR Medicamylasal intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions
Visual Changes (assessed from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

Systemic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cytokine Release Syndrome[9]	Mild signs and symptoms AND Therapy (i.e., antibody infusion) interruption not indicated	Therapy (i.e., antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤ 24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Fatigue or Malaise *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0 to < 38.6°C or 100.4 to < 101.5°F	≥ 38.6 to < 39.3°C or ≥ 101.5 to < 102.7°F	≥ 39.3 to < 40.0°C or ≥ 102.7 to < 104.0°F	≥ 40.0°C or ≥ 104.0°F
Pain[10] (not associated with study agent injections and not specified elsewhere) *Specify location*	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated
Serum Sickness[11]	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (e.g., antihistamines)	Severe signs and symptoms AND Higher level intervention indicated (e.g., steroids or IV fluids)	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Underweight[12] *> 5 to 19 years of age*	NA	WHO BMI z-score < -2 to ≤ -3	WHO BMI z-score < -3	WHO BMI z-score < -3 with life-threatening consequences

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
2 to 5 years of age	NA	WHO Weight-for-height z-score < -2 to ≤ -3	WHO Weight-for-height z-score < -3	WHO Weight-for-height z-score < -3 with life- threatening consequences
< 2 years of age	NA	WHO Weight-for-length z-score < -2 to ≤ -3	WHO Weight-for-length z-score < -3	WHO Weight-for-length z-score < -3 with life- threatening consequences
Weight Loss (excludes postpartum weight loss)	NA	5 to < 9% loss in body weight from baseline	≥ 9 to < 20% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)

[9] Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.
[10] For pain associated with injections or infusions, see the Site Reactions to Injections and Infusions section.
[11] Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.
[12] WHO reference tables may be accesed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007_bmi_for_age/en / for participants > 5 to 19 years of age and http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those ≤ 5 years of age.

Urinary

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Urinary Tract Obstruction	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life- threatening consequences

Site Reactions to Injections and Infusions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Injection Site Pain or Tenderness *Report only one*	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or Redness[13] *Report only one* *> 15 years of age*	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter OR ≥ 100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
≤ 15 years of age	≤ 2.5 cm in diameter	> 2.5 cm in diameter with < 50% surface area of the extremity segment involved (e.g., upper arm or thigh)	≥ 50% surface area of the extremity segment involved (e.g., upper arm or thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling *Report only one* *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
≤ 15 years of age	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in < 48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

[13] Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.

Laboratory Values

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acidosis	NA	pH ≥ 7.3 to < LLN	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to < LLN *30 to < LLN*	≥ 2.0 to < 3.0 *≥ 20 to < 30*	< 2.0 *< 20*	NA
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Alkalosis	NA	pH > ULN to ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT or SGPT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Creatine Kinase, High	3 to < 6 x ULN	6 to < 10 x ULN	10 to < 20 x ULN	≥ 20 x ULN
Creatinine, High	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase of > 0.3 mg/dL above baseline	> 1.8 to < 3.5 x ULN OR Increase of 1.5 to < 2.0 x above baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x above baseline
Creatinine Clearance 15 or eGFR, Low *Report only one*	NA	< 90 to 60 ml/min or ml/min/1.73 m^2 OR 10 to < 30% decrease from baseline	< 60 to 30 ml/min or ml/min/1.73 m2 OR ≥ 30 to < 50% decrease from baseline	< 30 ml/min or ml/min/1.73 m2 OR ≥ 50% decrease from baseline or dialysis needed
Glucose (mg/dL*; mmol/L)*				
Fasting, High	110 to 125 *6.11 to < 6.95*	> 125 to 250 *6.95 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	> 500 *≥ 27.75*
Nonfasting, High	116 to 160 *6.44 to < 8.89*	> 160 to 250 *8.89 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	> 500 *≥ 27.75*
Glucose, Low (mg/dL*; mmol/L)*				
≥ 1 month of age	55 to 64 *3.05 to 3.55*	40 to < 55 *2.22 to < 3.05*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
< 1 month of age	50 to 54 *2.78 to 3.00*	40 to < 50 *2.22 to < 2.78*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
Lactate, High	ULN to < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences
Lipase, High	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
Lipid Disorders (mg/dL*; mmol/L)*				
Cholesterol, Fasting, High				
≥ 18 years of age	200 to < 240 *5.18 to < 6.19*	240 to < 300 *6.19 to < 7.77*	≥ 300 *≥ 7.77*	NA
< 18 years of age	170 to < 200 4.40 to < 5.15	200 to < 300 5.15 to < 7.77	≥ 300 ≥ 7.77	NA
LDL, Fasting, High	130 to < 160	160 to < 190	≥ 190	NA

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
≥ 18 years of age	*3.37 to < 4.12*	*4.12 to < 4.90*	*≥ 4.90*	
> 2 to < 18 years of age	110 to < 130 *2.85 to < 3.34*	130 to < 190 *3.34 to < 4.90*	≥ 190 *≥ 4.90*	NA
Triglycerides, Fasting, High	150 to 300 *1.71 to 3.42*	>300 to 500 *>3.42 to 5.7*	>500 to < 1,000 *>5.7 to 11.4*	> 1,000 *> 11.4*
Magnesium[16], Low (mEq/L*; mmol/L)*	1.2 to < 1.4 *0.60 to < 0.70*	0.9 to < 1.2 *0.45 to < 0.60*	0.6 to < 0.9 *0.30 to < 0.45*	< 0.6 *< 0.30*
Phosphate, Low (mg/dL*; mmol/L)*				
> 14 years of age	2.0 to < LLN *0.81 to < LLN*	1.4 to < 2.0 *0.65 to < 0.81*	1.0 to < 1.4 *0.32 to < 0.65*	< 1.0 *< 0.32*
1 to 14 years of age	3.0 to < 3.5 *0.97 to < 1.13*	2.5 to < 3.0 *0.81 to < 0.97*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
< 1 year of age	3.5 to < 4.5 *1.13 to < 1.45*	2.5 to < 3.5 *0.81 to < 1.13*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
Potassium, High (mEq/L*; mmol/L)*	5.6 to < 6.0 *5.6 to < 6.0*	6.0 to < 6.5 *6.0 to < 6.5*	6.5 to < 7.0 *6.5 to < 7.0*	≥ 7.0 *≥ 7.0*
Potassium, Low (mEq/L*; mmol/L)*	3.0 to < 3.4 *3.0 to < 3.4*	2.5 to < 3.0 *2.5 to < 3.0*	2.0 to < 2.5 *2.0 to < 2.5*	< 2.0 *< 2.0*
Sodium, High (mEq/L*; mmol/L)*	146 to < 150 *146 to < 150*	150 to < 154 *150 to < 154*	154 to < 160 *154 to < 160*	≥ 160 *≥ 160*
Sodium, Low (mEq/L*; mmol/L)*	130 to < 135 *130 to < 135*	125 to < 130 *125 to < 135*	121 to < 125 *121 to < 125*	≤ 120 *≤ 120*
Uric Acid, High (mg/dL*; mmol/L)*	7.5 to < 10.0 *0.45 to < 0.59*	10.0 to < 12.0 *0.59 to < 0.71*	12.0 to < 15.0 *0.71 to < 0.89*	≥ 15.0 *≥ 0.89*

[14]Direct bilirubin > 1.5 mg/dL in a participant < 28 days of age should be graded as grade 2, if < 10% of the total bilirubin.
[15]Use the applicable formula (i.e., Cockroft-Gault in mL/min or Schwatrz in mL/min/1.73m^2).
[16]To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.

Haematology

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Absolute CD4+ Count, Low (cell/mm^3; *cells/L*) *> 5 years of age (not HIV infected)*	300 to < 400 *300 to < 400*	200 to < 300 *200 to < 300*	100 to < 200 *100 to < 200*	< 100 *< 100*
Absolute Lymphocyte Count, Low (cell/mm^3; *cells/L*) *> 5 years of age (not HIV infected)*	600 to < 650 *0.600 x 10^9 to < 0.650 x 10^9*	500 to < 600 *0.500 x 10^9 to < 0.600 x 10^9*	350 to < 500 *0.350 x 10^9 to < 0.500 x 10^9*	< 350 *< 0.350 x 10^9*
Absolute Neutrophil Count (ANC), Low (cells/mm^3; *cells/L*) *> 7 days of*	800 to 1,000 *0.800 x 10^9 to 1.000 x 10^9*	600 to 799 *0.600 x 10^9 to 0.799 x10^9*	400 to 599 *0.400 x 10^9 to 0.599 x10^9*	< 400 *< 0.400 x 10^9*
2 to 7 days of age	1,250 to 1,500 *1.250 x 10^9 to 1.500 x 10^9*	1,000 to 1,249 *1.000 x 10^9 to 1.249 x10^9*	750 to 999 *0.750 x 10^9 to 0.999 x10^9*	< 750 *< 0.750 x 10^9*
≤ 1 day of age	4,000 to 5,000 *4.000 x 109 to 5.000 x 10^9*	3,000 to 3,999 *3.000 x 10^9 to 3.999 x10^9*	1,500 to 2,999 *1.500 x 10^9 to 2.999 x10^9*	< 1,500 *< 1.500 x 10^9*
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to < 200 *1.00 to < 2.00* OR 0.75 to < 1.00 x LLN	75 to < 100 *0.75 to < 1.00* OR ≥ 0.50 to < 0.75 x LLN	50 to < 75 *0.50 to < 0.75* OR 0.25 to < 0.50 x LLN	< 50 *< 0.50* OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin[17], Low (g/dL; *mmol/L*)[18] *≥ 13 years of age (male only)*	10.0 to 10.9 *6.19 to 6.76*	9.0 to < 10.0 *5.57 to < 6.19*	7.0 to < 9.0 *4.34 to < 5.57*	< 7.0 *< 4.34*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
≥ 13 years of age (female only)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
57 days of age to < 13 years of age (male and female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
36 to 56 days of age (male and female)	8.5 to 9.6 *5.26 to 5.99*	7.0 to < 8.5 *4.32 to < 5.26*	6.0 to < 7.0 *3.72 to < 4.32*	< 6.0 *< 3.72*
22 to 35 days of age (male and female)	9.5 to 11.0 *5.88 to 6.86*	8.0 to < 9.5 *4.94 to < 5.88*	6.7 to < 8.0 *4.15 to < 4.94*	< 6.7 *< 4.15*
8 to ≤ 21 days of age (male and female)	11.0 to 13.0 *6.81 to 8.10*	9.0 to < 11.0 *5.57 to < 6.81*	8.0 to < 9.0 *4.96 to < 5.57*	< 8.0 *< 4.96*
≤ 7 days of age (male and female)	13.0 to 14.0 *8.05 to 8.72*	10.0 to < 13.0 *6.19 to < 8.05*	9.0 to < 10.0 *5.59 to < 6.19*	< 9.0 *< 5.59*
INR, High (not on anticoagulation therapy)	1.1 to < 1.5 x ULN	1.5 to < 2.0 x ULN	2.0 to < 3.0 x ULN	≥ 3.0 x ULN
Methemoglobin (% hemoglobin)	5.0 to < 10.0%	10.0 to < 15.0%	15.0 to < 20.0%	≥ 20.0%
PTT, High (not on anticoagulation	1.1 to < 1.66 x ULN	1.66 to < 2.33 x ULN	2.33 to < 3.00 x ULN	≥ 3.00 x ULN
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to < 124,999 *100.000 x 10^9 to < 124.999 x 10^9*	50,000 to < 100,000 *50.000 x 10^9 to < 100.000 x 10^9*	25,000 to < 50,000 *25.000 x 10^9 to < 50.000 x 10^9*	< 25,000 *< 25.000 x 10^9*
PT, High (not on anticoagulation therapy)	1.1 to < 1.25 x ULN	1.25 to < 1.50 x ULN	1.50 to < 3.00 x ULN	≥ 3.00 x ULN
WBC, Decreased (cells/mm^3*; cells/L*) *> 7 days of age*	2,000 to 2,499 *2.000 x 10^9 to 2.499 x 10^9*	1,500 to 1,999 *1.500 x 10^9 to 1.999 x10^9*	1,000 to 1,499 *1.000 x 10^9 to 1.499 x10^9*	< 1,000 *< 1.000 x 10^9*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
≤ 7 days of age	5,500 to 6,999 *5.500 x 10^9 to 6.999 x 10^9*	4,000 to 5,499 *4.000 x 10^9 to 5.499 x 10^9*	2,500 to 3,999 *2.500 x 10^9 to 3.999 x10^9*	< 2,500 *< 2.500 x 10^9*

[17]Male and female sex are defined as sex at birth.
[18]The conversion factor used to convert g/dL to mmol/L is 0.6206 and is the most commonly used conversion factor. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using the appropriate conversion factor for the particular laboratory.

Urinalysis

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	NA
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to < 10 RBCs per high power field	≥ 10 RBCs per high power field	Gross, with or without clots OR With RBC casts OR Intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA

Reference

U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0. [November 2014]. Available from: http://rsc.tech-res.com/Document/safetyandpharmacovigilance/DAIDS_AE_GRADING_TABLE_v2_NOV2014.pdf (accessed 10 September 2015)

12.7. Appendix 7: Definition of and Procedures for Recording, Evaluating, Follow-up and Reporting of Adverse Events

12.7.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • 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 prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected 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 this is an intentional overdose taken with possible suicidal/self-harming intent. This 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. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

Events <u>NOT</u> meeting definition of an AE include:
• 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 subject'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 subject's

condition.

- Medical or surgical procedure (e.g. endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where 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.

12.7.2. Definition of Serious Adverse Events

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

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE:

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject 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 hospitalisation or prolongation of existing hospitalisation

NOTE:

- In general, hospitalisation signifies that the subject 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 out-patient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.
- Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity

NOTE:

- 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, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere 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 reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. • Examples of such events are 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 hospitalisation, or development of drug dependency or drug abuse
g. Is associated with liver injury <u>and</u> 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 subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

12.7.3. 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: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension

- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularisation

12.7.4. Sentinel Events

Sentinel Event Definition:

A sentinel event is a GSK-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. 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-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)

12.7.5. Recording of AEs and SAEs

AEs and SAE Recording:

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE/SAE in the CRF
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to

submission of to GSK.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

12.7.6. Evaluating AEs and SAEs

Assessment of Intensity:

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the categories in the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE Grading Table") in Appendix 6: Division of AIDS table for Grading Severity of Adult and Pediatric Adverse Events, Section 12.6:

- Grade1 / Mild
- Grade 2 / Moderate
- Grade 3 / Severe
- Grade 4 / Potentially life threatening
- Grade 5 / Death
- 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 the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence 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 natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in the determination of 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 when an SAE has occurred and the investigator has minimal

information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to ViiV Healthcare/GSK/PPD.**

- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs:

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

12.7.7. Reporting of SAEs and other events to ViiV Healthcare/GSK/PPD

Reporting of SAEs and other events to ViiV Healthcare/GSK/PPD:

- Primary mechanism for reporting SAEs to the Medical Monitor will be the electronic data collection tool.
- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it (or scan and email it) to the Medical Monitor.
- Site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE.
- After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) 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 subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor by telephone.
- Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

	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	2 weeks	"Pregnancy Notification Form"	2 weeks	"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]
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 subject 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. Appendix 8: Toxicity Management

Adverse events that occur during the trial should be evaluated by the investigator and graded according to the DAIDS toxicity scales (see Section 12.6). Additional information regarding detecting, documenting and reporting AEs and SAEs are available in Section 12.7.

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 subject 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 subject's eCRF.

Grade 1 or Grade 2 Toxicity/Adverse Event

Subjects who develop a Grade 1 or Grade 2 AE or toxicity may continue study treatment at the discretion of the investigator. Subjects 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

Subjects 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.

Subjects 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 subject, study treatment should be permanently discontinued and the subject withdrawn from study. Subjects 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.

Subjects 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 12.8.1.7 and rash in Section 12.8.1.6.

Grade 4 Toxicity/Adverse Event

Subjects 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. Subjects should be rechecked each week until the AE returns to Grade 2.

Subjects 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.

Subjects 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 12.8.1.7. An in-clinic Follow-up visit will be conducted approximately 4 weeks after the last dose of study medication for subjects with ongoing AEs, and SAEs and also any laboratory abnormalities that are considered to be AEs or potentially harmful to the subject, at the last on-study visit.

12.8.1. 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.

Subjects 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 Appendix 7, Section 12.7.

12.8.1.1. Liver Chemistry Stopping and Follow-up Criteria

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event aetiology during administration of study drug and the follow-up period. For a complete listing of stopping and follow-up criteria refer to Appendix 3, Section 12.3.

12.8.1.2. Restarting Study Drug

Refer to Appendix 4, Section 12.4 for details on drug restart following transient resolving liver events not related to study treatment.

12.8.1.3. Decline in Renal Function

Subjects who experience an increase in serum creatinine from Baseline of 45 micromoles/litre (µMol/L) (or 0.5 milligrams/decilitre [mg/dL]) should return for a confirmatory assessment within 2 to 4 weeks. A urinalysis and urine albumin/creatinine and urine total protein/albumin ratios should also be done at this confirmatory visit. If the creatinine increase is confirmed, the investigator should contact the study Medical Monitor to discuss additional follow-up and medical management.

Subjects who experience progression to an estimated GFR (using the CKD-EPI method) of <50 mL/min/1.73 m^2 must return for a confirmatory assessment within 2 weeks [Levey, 2009]. A urinalysis and urine albumin/creatinine and urine protein/creatinine ratios should be done at this confirmatory visit. If an estimated GFR of <50 mL/min/1.73 m^2 is confirmed, then study treatment should be discontinued and the subject withdrawn from the study (as dose adjustment is needed for NRTIs, which is not possible in this blinded study).

Proximal Renal Tubule Dysfunction

Proximal Renal Tubule Dysfunction (PRTD) is defined as:

- Confirmed rise in serum creatinine of ≥0.5 mg/dL from Baseline AND serum phosphate <2.0 mg/dL;
- Either of the above accompanied by any two of the following:
- Glycosuria (≥250 mg/dL) in a non-diabetic;
- Low serum potassium (<3 mEq/L);
- Low serum bicarbonate (<19 mEq/L).

Subjects meeting criteria for PRTD must return for a confirmatory assessment within 2 weeks of diagnosis. A urinalysis should also be performed at the time of the confirmatory assessment. If PRTD is confirmed subjects must be withdrawn from the study.

12.8.1.4. Proteinuria

Subjects with an abnormal urine albumin/creatinine ratio (>0.3 mg/mg, >300 mg/g, or >34 mg/mmol) that represents a change from Baseline and no associated increase in creatinine, should have a repeat spot urine albumin/creatinine ratio performed within 2-4 weeks. If confirmed, then consideration should be given to additional evaluation after consultation with the study Medical Monitor. Additional evaluation may include a 24-hour urine protein and creatinine measurement and nephrology referral.

Subjects with an abnormal urine albumin/creatinine ratio (>0.3 mg/mg, 300 mg/g, or >34 mg/mmol and representing a change from Baseline) and a serum creatinine increase >45 µmol/L (or 0.5 mg/dL) should have confirmation of both results within 2 weeks. If confirmed, the study Medical Monitor should be contacted immediately. Agreement on further management should be agreed between the investigator and Medical Monitor.

12.8.1.5. Allergic reaction

Subjects may continue study drug for Grade 1 or 2 allergic reactions at the discretion of the Investigator. The subject 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.

Subjects 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 subject should be withdrawn from the study. Subjects should be treated as clinically appropriate and followed until resolution of the AE.

12.8.1.6. 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 RM2007/00683/11].

Subjects with an isolated Grade 1 rash may continue study drug at the Investigator's discretion. The subject 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.

Subjects 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 subject 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.

Subjects 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 subject should be withdrawn from the study. Subjects 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, Appendix 6, Section 12.6).

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.

12.8.1.7. Hypertriglyceridemia/Hypercholesterolemia

Samples for lipid measurements must be obtained in a fasted state according to the Time and Events Table (Section 7.1). Subjects who experience asymptomatic triglyceride or cholesterol elevations may continue to receive study drug.

12.8.1.8. 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 subject 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 subject withdrawn from the study.

References

GlaxoSmithKline Document Number RM2007/00683/11: GSK1349572 Clinical Investigator's Brochure, version 09. October 2015.

Levey AS, Stevens LA, Schmid CH, et.al. A new equation to estimate glomerular filtration rate. Ann Int Med. 2009; 150: 604-612.

12.9. Appendix 9: Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information

12.9.1. 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 subjects 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.

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 subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011]. The documentation on male sterility can come from the site personnel's review of subject's medical records, medical examination, and/or semen analysis, or medical history interview provided by her or her partner.

In addition, male condom combined with a vaginal spermicide (foam, gel, film, cream, or suppository) [Hatcher, 2011] is included in this study as a permitted method of contraception.

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 subjects understand how to properly use these methods of contraception.

12.9.2. Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to ViiV Healthcare/GSK/PPD within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, 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 will also 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 foetal 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 the Medical Monitor as described in Appendix 7, Section 12.7. 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 subject 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, et al, editors. Contraceptive Technology. 20th edition. Atlanta, Georgia: Ardent Media, Inc., 2011: 50. Table 3-2.

12.10. Appendix 10: Country-specific Requirements

United Kingdom

This requirement has been included based on requests from the Medicines and Healthcare products Regulatory Agency (MHRA) to include information on the specific duration of the Continuation Phase/Study Treatment for similar Phase III trials being conducted with dolutegravir.

Study Duration

In this study, the date of last study treatment administration in the UK will be determined by the completion of the 148 week randomised phase of the study for the last UK subject enrolled (it will not be determined by the completion of the Continuation Phase). The last subject will be enrolled by March 2017, and hence the last study treatment administration will occur by January 2020. (Note: The Continuation Phase is intended to provide subjects randomised to DTG plus 3TC with post-study access to DTG plus 3TC until the DTG plus 3TC is approved as a dual regimen in their local countries. For subjects in the UK, the Continuation Phase is anticipated to conclude by December 2020, when the dual regimen of DTG plus 3TC is anticipated to be approved).

12.11. Appendix 11: Protocol Changes

Protocol Amendment 01

This global amendment is applicable to all participating sites.

Summary of Changes in Protocol Amendment 01 and Rationale:

- The double barrier method of contraception (male condom combined with a vaginal spermicide) was added in this study as a permitted method for preventing pregnancy in females of reproductive potential. All study medications have full marketing approval, and based on animal studies, have a very low risk for embryofetal toxicity. The use of the double barrier method is considered to be an acceptable method of contraception with very low failure rates.

- Exclusion criterion #15 (limitations on investigational drug use) was broadened to include additional countries as needed. Inclusion of Portugal was required by the Portuguese National Ethics Committee for Clinical Research.

- Assessment of weight at Weeks 96 and 144 was added to monitor the incidence of significant weight gain with dolutegravir use.

- Assessment of inflammation biomarkers (IL-6, hs-CRP), at Day 1, and Weeks 48, 96 and 144, was added as a new exploratory endpoint. Elevated levels of inflammation may be associated with the occurrence of non-AIDS-defining events such as cardiovascular disease, liver disease and cancer. Changes from Baseline between the 2-drug and 3-drug regimen will be evaluated.

- Assessment of telomere length at Day 1, and Weeks 96 and 144, was added as a new exploratory endpoint. Telomere length may be a marker for accelerated aging, and perturbations in this marker may be associated with aging-related morbidities. Where possible, changes from Baseline between the 2-drug and 3-drug regimen will be evaluated.

- For clarification purposes, the ‘peripheral blood mononuclear cell (PBMC)’ sample in Section 7.1 (Time and Events table) and Section 7.6.1 (HIV-1 Exploratory Analyses) was renamed as a ‘whole blood’ sample.

- The Day 1 ‘PBMC’ sample (now named ‘whole blood’ sample) originally designated for virology use was additionally designated for telomere length measurement, where possible. Additional whole blood samples were added for measurement of telomere length at Week 96 and Week 144.

- A description of commercial image dolutegravir tablets was added to Section 6.1 (Investigational Product and Other Study Treatment) to allow use of commercial material as well as clinical trial material during the study.

- The physical description for open-label lamivudine in Section 6.1 was corrected.

- To correct an omission, standard procedures for forwarding pregnancy information to the Antiretroviral Pregnancy Register were added.

- For clarification purposes, the AE severity gradings in Appendix 7, Section 12.7.6 (Evaluating AEs and SAEs) were updated to be consistent with Appendix 6, Section 12.6. (Division of AIDS table for Grading Severity of Adult and Pediatric Adverse Events). This change has no impact on the investigator's evaluation of adverse events.

- Minor revisions were made to the text to provide updated information, correct errors and improve accuracy.

LIST OF SPECIFIC CHANGES

Unless stated otherwise, new text is represented in bold font, and deleted text in strikethrough font.

- **Authors**

Amended text:

PPD

- **Medical monitor/Sponsor Information Page**

Amended text

Secondary Medical Monitor	PPD			ViiV Healthcare 980 Great West Road, Brentford, Middlesex, TW8 9GS, UK ~~Mailstop UP4410 Collegeville, PA (USA)~~
	MD			

- **Section 1. Protocol Synopsis; Overall Design**

Amended text:

The study initially will enrol approximately 100 subjects with a Screening HIV-1 RNA of 1000 to ≤100,000 c/mL. Accumulated data from other clinical trials investigating the DTG plus 3TC dual regimen will undergo independent review. If the independent review is supportive of evaluating the dual regimen's efficacy in subjects with a Screening viral

load of up to 500,000 c/mL, recruitment will be opened to subjects with a Screening HIV-1 RNA of 1000 to ≤500,000 c/mL. If the review does not support enrolment of such subjects, the Screening viral load will remain capped at ≤100,000 c/mL. **This independent review of accumulated data on the DTG plus 3TC dual regimen was supportive, enabling an increase in the Screening viral load cap to ≤500,000 c/mL for subjects screened on/after 5 November 2016.**

- **Section 2.1. Study Rationale**

Amended text:

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 [BHIVA, 2015; DHHS, 2016; EACS, 2015; IAS-USA, 2014]. While these regimens are highly efficacious and generally well tolerated, there is growing concern about long-term toxicities, and great interest from patients and clinicians in unique regimens that might avoid such toxicities, and to provide effective long-term ART with the most streamlined regimens possible.

Contemporary potent 3-drug antiretroviral treatment has led to remarkable declines in morbidity and mortality in treated HIV-infected persons. However, this longer life expectancy has been accompanied by higher rates of non-acquired immuno-deficiency syndrome (AIDS)-defining events such as cardiovascular disease, liver disease and cancer. These non-AIDS-defining events are now the leading causes of morbidity and mortality among treated HIV-infected persons. The aetiologies of these non-AIDS-defining events are multi-factorial and may include chronic inflammation and immune activation, behavioural and lifestyle related factors, co-morbidities and the adverse effects of ART. In addition, as HIV-infected persons live longer, aging-associated co-morbidities are being seen with greater frequency, and this multi-morbidity often requires concomitant use of other medications. As ART needs to be taken life long, there is an unmet need for streamlined regimens that can minimize antiretroviral-related long-term toxicities and drug-drug interactions while maintaining viral suppression. Even modest improvements in side effects will have a big impact on the tolerability of, and adherence to life-long treatment regimens.

Two-drug antiretroviral regimens may maintain virologic suppression while minimizing the adverse effects from cumulative drug exposure and preserving future antiretroviral treatment options. While contemporary regimens avoid many of the liabilities of older agents, the consequences of long-term exposure to a 2-NRTI backbone remain uncertain. Chronic exposure to NRTIs may lead to telomerase and mitochondrial dysfunction, processes that may lead to accelerated aging, lipodystrophy, steatohepatitis and other aging-related morbidities [Solomon, 2014]. NRTIs have been linked to reduced telomerase activity in peripheral blood mononuclear cells (PBMCs) from HIV-infected patients [Leeansyah, 2013]. Of a multitude of NRTIs studied in vitro, tenofovir at therapeutic concentrations was

found to produce the most significant inhibition of telomerase leading to accelerated shortening of telomere length in activated PBMCs [Leeansyah, 2013; Stella-Ascariz, 2017].

- **Section 2.2. Brief Background**

Amended text:

Limited data are also available from two pilot studies to evaluate the dual regimen of DTG plus 3TC:

- An ~~ongoing~~ investigator-initiated 48-week pilot study, the PADDLE trial (NCT02211482), ~~is being~~ **has been** conducted in 20 HIV treatment-naïve subjects with no genotypic resistance to 3TC and a viral load of ≤100,000 c/mL at Screening and has provided notable early data on the efficacy of a once-daily DTG plus 3TC two-drug regimen. Subjects 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. By Week 8, all 20 subjects, including 4 subjects with a Baseline HIV-1 RNA of >100,000 c/mL, had reached a viral load of <50 c/mL and all maintained virologic suppression through Week 24 [Figueroa, 2015]. **At Week 48, 18/20 (90%) of subjects achieved the primary endpoint of plasma HIV-1 RNA <50 copies/mL using the FDA snapshot algorithm for the intention to treat – exposed (ITT-E) population [Cahn, 2017].**

- **The ongoing ACTG A5353 trial is a Phase II, single-arm pilot study of once-daily DTG plus 3TC in treatment-naïve HIV-1-infected participants with a viral load of ≥1000 to <500,000 c/mL. Virologic efficacy (plasma HIV-1 RNA <50 c/mL using the FDA Snapshot) at Week 24 was 108/120 (90%) with no significant difference between the low (≤100,000 c/mL) and high (>100,000 c/mL) viral load strata: 90% and 89%, respectively [Taiwo, 2017].**

- **Section 3. Objectives and Endpoints**

- **Additional text:**

Objectives	Endpoints
Exploratory	
• **To evaluate inflammation biomarkers in subjects treated with DTG+ 3TC compared to DTG + TDF/FTC**	• **Change from Baseline in inflammation biomarkers at Weeks 48, 96 and 144**
• **To evaluate telomere length in subjects treated with DTG + 3TC compared to DTG + TDF/FTC**	• **Change from Baseline in telomere length at Weeks 96 and 144**

- **Section 4.1. Overall Design, and Section 4.3. Type and Number of Subjects**

Amended text:

The study initially will enrol approximately 100 subjects with a Screening HIV-1 RNA of 1000 to ≤100,000 c/mL. Accumulated data from other clinical trials investigating the DTG plus 3TC dual regimen will undergo independent review. If the independent review is supportive of evaluating the dual regimen's efficacy in subjects with a Screening viral load of up to 500,000 c/mL, recruitment will be opened to subjects with a Screening HIV-1 RNA of 1000 to ≤500,000 c/mL. If the review does not support enrolment of such subjects, the Screening viral load will remain capped at ≤100,000 c/mL. **This independent review of accumulated data on the DTG plus 3TC dual regimen was supportive, enabling an increase in the Screening viral load cap to ≤500,000 c/mL for subjects screened on/after 5 November 2016.**

- **Section 5.2. Exclusion Criteria**

Amended text:

15. Subjects enrolled in France **(and other countries as required by local regulations or ethics committees/IRBs)**: the subject has participated in any study using an investigational drug during the previous 60 days or 5 half-lives, or twice the duration of the biological effect of the experimental drug or vaccine, whichever is longer, prior to screening for the study or the subject will participate simultaneously in another clinical study.

- **Section 6.1. Investigational Product and Other Study Treatment**

Amended text:

	Study Treatment (Double-blind Randomised Phase, Day 1 to Week 96)		
Product name:	Dolutegravir, DTG	Lamivudine, 3TC	Tenofovir disoproxil fumarate/emtricitabine fixed-dose combination, TDF/FTC FDC
Formulation description:	**Commercial supply or** Clinical trial material, which is the same formulation as the commercial material with the exception of the film coat colour	Over-encapsulated commercial supply tablet to visually match over-encapsulated TDF/FTC FDC tablet	Over-encapsulated commercial supply tablet to visually match over-encapsulated 3TC tablet
Dosage form:	Tablet	Capsule	Capsule
Unit dose strength(s)/Dosage level(s):	50 mg	300 mg	300 mg TDF/200 mg FTC
Route of Administration:	Oral	Oral	Oral
Dosing instructions:	Take one tablet once daily with or without food	Take one capsule once daily with or without food	Take one capsule once daily with or without food
Physical description:	**Commercial supply: Yellow, round, film-coated, biconvex tablets debossed with "SV 572" on one side and "50" on the other side. The tablets are packaged into HDPE bottles with induction seals and child-resistant closures, each containing 30 tablets.** **Clinical trial supply:** White, round, biconvex, film-coated tablets debossed on one side with "SV 572" and on the other side with "50". The tablets are packaged into high density polyethylene (HDPE) bottles with induction seals and child-resistant closures. Each 45 ml bottle contains 30 tablets and a desiccant.	Swedish Orange, size AA elongated double-blind hydroxypropyl methylcellulose (HPMC) capsules. The capsules are packaged into HDPE bottles with induction seals and child- resistant closures. Each 150 mL bottle contains 30 capsules and a desiccant.	Swedish Orange, size AA elongated double-blind HPMC capsules. The capsules are packaged into HDPE bottles with induction seals and child-resistant closures. Each 150 mL bottle contains 30 capsules and a desiccant.

	Study Treatment (Open-label Randomised Phase, Week 96 to Week 148)		
Product name:	Dolutegravir, DTG	Lamivudine, 3TC	Tenofovir disoproxil fumarate/emtricitabine fixed-dose combination, TDF/FTC FDC
Formulation description:	**Commercial supply or** Clinical trial material, which is the same formulation as the commercial material with the exception of the film coat colour	Commercial supply	Commercial supply
Dosage form:	Tablet	Tablet	Tablet
Unit dose strength(s)/Dosage level(s):	50 mg	300 mg	300 mg TDF/200 mg FTC
Route of Administration:	Oral	Oral	Oral
Dosing instructions:	Take one tablet once daily with or without food	Take one tablet once daily with or without food	Take one tablet once daily with or without food
Physical description:	**Commercial supply: Yellow, round, film-coated, biconvex tablets debossed with "SV 572" on one side and "50" on the other side. The tablets are packaged into HDPE bottles with induction seals and child-resistant closures, each containing 30 tablets.** **Clinical trial supply:** White, round, biconvex, film-coated tablets debossed on one side with "SV 572" and on the other side with "50". The tablets are packaged into HDPE bottles with induction seals and child-resistant closures. Each 45 ml bottle contains 30 tablets and a desiccant.	**Gray, diamond-shaped, film-coated tablets engraved with "GX EJ7" on one side and plain on the reverse side.** ~~White, diamond-shaped, scored, film-coated tablets debossed with "GX CJ7" on both sides.~~ The tablets are packed in**to** ~~over-labelled~~ HDPE bottles with child-resistant closures each containing 30 tablets.	Blue, capsule-shaped, film-coated tablet, debossed on one side with "GILEAD" and on the other side with "701". The tablets are packed in over-labelled HDPE bottles with polypropylene child-resistant closures each containing 30 tablets and a desiccant.

	Study Treatment (Continuation Phase)	
Product name:	Dolutegravir, DTG	Lamivudine, 3TC
Formulation description:	**Commercial supply** **or** Clinical trial material, which is the same formulation as the commercial material with the exception of the film coat colour	Commercial supply
Dosage form:	Tablet	Tablet
Unit dose strength(s)/Dosage level(s):	50 mg	300 mg
Route of Administration:	Oral	Oral
Dosing instructions:	Take one tablet once daily with or without food	Take one tablet once daily with or without food
Physical description:	**Commercial supply:** **Yellow, round, film-coated, biconvex tablets debossed with "SV 572" on one side and "50" on the other side. The tablets are packaged into HDPE bottles with induction seals and child-resistant closures, each containing 30 tablets.** **Clinical trial supply:** White, round, biconvex, film-coated tablets debossed on one side with "SV 572" and on the other side with "50". The tablets are packaged into HDPE bottles with induction seals and child-resistant closures. Each 45 ml bottle contains 30 tablets and a desiccant.	**Gray, diamond-shaped, film-coated tablets engraved with "GX EJ7" on one side and plain on the reverse side**. ~~White, diamond-shaped, scored, film-coated tablets debossed with "GX CJ7" on both sides.~~ The tablets are packed in**to** ~~over-labelled~~ HDPE bottles with child-resistant closures each containing 30 tablets.

- **Section 7.1. Time and Events Table**

The Time and Events Table was amended as follows:

- Assessment of weight was added at Weeks 96 and 144.
- Assessment of inflammation biomarkers (IL-6, hs-CRP) was added at Day 1, and Weeks 48, 96 and 144.
- The 'peripheral blood mononuclear cell (PBMC)' sample was renamed as a 'whole blood' sample.
- The Day 1 'PBMC' sample (now renamed 'whole blood' sample) will also be used for telomere length measurement, where possible.
- Additional whole blood samples were added for measurement of telomere length at Weeks 96 and 144.
- Addition of footnote 'v' required original footnote 'v' to be renamed footnote 'w'.

Amended text:

Procedures	Screening Visit[a]	Double-blind Randomised Phase													Open-label Randomised Phase						Continuation Phase[c]	Withdrawal	Follow-up[d]
		Baseline / Day 1	Week 4	8	12	16	24	28[b]	36	48	52[b]	60	72	84	96	100[b]	108	120	132	144	148	Every 12 weeks after Week 148		
Clinical and Other Assessments																								
Written informed consent	X																							
Inclusion/Exclusion criteria[e]	X	X																						
Demography	X																							
Prior ART history	X																							
Medical history[f]	X																							
Current medical conditions	X																							
Cardiovascular risk assessment, including vital signs[g]	X														**X**					**X**				
HIV risk factors and mode of transmission		X																						
CDC HIV-1 classification	X	X																						
HIV associated conditions			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Columbia Suicidality Severity Rating Scale		X[h]	X	X	X	X	X		X	X		X	X	X	X		X	X	X	X		X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Symptom Directed Physical Exam/Medical Decision Making[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
12-lead ECG[j]	X																								

Procedures	Screening Visit[a]	Double-blind Randomised Phase														Open-label Randomised Phase						Continuation Phase[c]	Withdrawal	Follow-up[d]
		Baseline / Day 1	Week																			Every 12 weeks after Week 148		
			4	8	12	16	24	28[b]	36	48	52[b]	60	72	84	96	100[b]	108	120	132	144	148			
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious adverse events	X[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EQ-5D-5L[l]		X	X				X			X					X					X			X	
Laboratory Assessments																								
Plasma for HIV genotyping	X																							
Quantitative plasma HIV-1 RNA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[m]	X	X	
Lymphocyte subset	X	X	X	X	X	X	X		X	X		X	X	X	X		X	X	X	X	X		X	
Plasma for storage**/inflammation biomarkers**[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical chemistry	X	X	X	X	X	X	X		X	X		X	X	X	X		X	X	X	X	X		X	X
Haematology	X	X	X	X	X	X	X		X	X		X	X	X	X		X	X	X	X	X		X	X
PT/INR	X																							
Fasting lipids and glucose[o]		X					X			X					X					X			X[p]	
Urinalysis and spot urine for protein analysis[q]		X					X			X					X					X			X	X
Pregnancy test[r]	S	U	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	
HBsAg, anti-HBc, anti-HBs, and HBV DNA[s]	X																							
HCV antibody	X																							
RPR	X																							

Procedures	Screening Visit[a]	Double-blind Randomised Phase													Open-label Randomised Phase						Continuation Phase[c]	Withdrawal	Follow-up[d]
		Baseline / Day 1	Week																				
			4	8	12	16	24	28[b]	36	48	52[b]	60	72	84	96	100[b]	108	120	132	144	148	Every 12 weeks after Week 148		
Renal and bone marker analytes (blood/urine)[t]		X					X			X					X					X			X	
~~PBMCs~~**Whole blood for virology/telomere length**[u]		X[u]																			X[u]		X[u]	
Whole blood for telomere length[v]															**X**					**X**				
Study Treatment																								
IVRS/IWRS[vw]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study treatment		X	X	X	X	X	X		X	X		X	X	X	X		X	X	X	X	X	X		
Study treatment accountability (pill counts)			X	X	X	X	X		X	X		X	X	X	X		X	X	X	X	X	X	X	

anti-HBc = antibody to hepatitis B core antigen, anti-HBs = hepatitis B surface antibody, ART = antiretroviral therapy, CDC = Centers for Disease Control and Prevention, DNA = deoxyribonucleic acid, ECG = electrocardiograph, HBsAg = hepatitis B surface antigen, HCV = hepatitis C virus, HIV-1 = human immunodeficiency virus type 1, INR = international normalised ratio, IVRS = interactive voice recognition system, IWRS = interactive web recognition system, ~~PBMC = peripheral blood mononuclear cell,~~ PT = prothrombin time, RNA = ribonucleic acid, RPR = rapid plasma reagin

a. Randomisation may occur as soon as all Screening results are available.

b. Subjects with plasma HIV-1 RNA levels ≥50 c/mL at Week 24, Week 48 and Week 96 must have HIV-1 levels re-assessed by a second measurement performed four weeks later at the Week 28, Week 52 visit and Week 100 visit, respectively. Subjects should have received full doses of study treatment for at least 2 weeks at the time of HIV-1 RNA re-assessment for any HIV-1 RNA level ≥50 c/mL. Subjects with plasma HIV-1 RNA levels <50 c/mL at Week 24, Week 48 and Week 96 should not attend the Week 28 visit, Week 52 visit and Week 100 visit, respectively.

c. Subjects randomised to DTG plus 3TC who complete through Week 148 may enter the Continuation Phase. Subjects completing the Continuation Phase must return to the clinic for an End of Continuation Phase visit when transitioning to commercial supplies or to an alternate ART regimen if appropriate. At this visit, conduct study assessments as specified for all Continuation Phase visits with the exception of dispensing study treatment.

d. An in-clinic Follow-up visit will be conducted 4 weeks after the last dose of study medication for subjects with the following conditions at the last on-study visit: ongoing AEs, serious adverse events (SAEs) regardless of attributability, any laboratory abnormalities considered to be AEs or potentially harmful to the subject.
e. 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.
f. Full medical history will be conducted prior to randomisation 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.
g. A**t Screening, a**ssessment for cardiovascular risk will include height, weight, blood pressure, smoking status and history, pertinent medical conditions (e.g., hypertension, diabetes mellitus), and family history of premature cardiovascular disease. Body mass index (BMI) will be calculated within the eCRF. **At Week 96 and Week 144, only weight will be measured.**
h. On Day 1, the electronic Columbia Suicidality Severity Rating Scale (eC-SSRS) is to be administered prior to randomisation.
i. Limited physical examination to include blood pressure at Day 1 (recorded in eCRF) for Framingham score assessment. Blood pressure to be measured after resting in a semi-supine position for at least 5 minutes.
j. A 12-lead ECG will be performed after resting in a semi-supine position for at least 5 minutes.
k. Only SAEs related to study participation or to a concomitantly administered ViiV Healthcare/GSK product will be collected between obtaining informed consent and administration of study drug at Day 1.
l. The questionnaire is recommended to be administered at the beginning of the visit before any other assessments are conducted. Only conduct the questionnaire at Withdrawal if occurring prior to Week 144.
m. At Week 148, repeat HIV-1 RNA testing will only be performed for subjects with HIV-1 RNA ≥50 c/mL at Week 144.
n. Plasma samples for storage will be collected at each visit, including unscheduled visits (e.g. for HIV-1 RNA levels and immunological parameters). Additionally, these samples will be used when needed such as when samples are lost or arrive at the laboratory unevaluable or as a priority need for genotypic and/or phenotypic analyses when subjects meet CVW criteria. **Additionally, inflammation biomarkers (IL-6, hs-CRP) will be measured at Day 1, Week 48, Week 96 and Week 144 using stored plasma samples.**
o. An overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable.
p. Only collect fasting lipids and glucose if the Withdrawal visit occurs at Week 24, Week 48, Week 96 or Week 144.
q. A morning specimen is preferred. To assess renal biomarkers: urine albumin/creatinine ratio; urine protein/creatinine ratio; and urine phosphate.
r. 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.
s. HBV DNA testing will be performed for subjects with positive anti-HBc and negative HBsAg and negative anti-HBs (past and/or current evidence). Subjects will have to return to the clinic to provide a sample for HBV DNA testing prior to randomisation.
t. Blood samples for renal and bone biomarker assessments: Renal**:** Cystatin C; Beta-2 Microglobulin; Retinol Binding Protein (RBP); Bone**:** bone specific alkaline phosphatase, procollagen type I N-terminal propeptide, type I collagen cross-linked C-telopeptide, osteocalcin, 25-hydroxyvitamin D. Urine sample for renal biomarker assessments: RBP and Beta-2-Microglobulin. Only collect at the Withdrawal visit if it occurs at Week 24, Week 48, Week 96 or Week 144.
u. Whole blood~~PBMC collection~~ samples may be used for virologic analyses as described in the protocol~~. A~~**; a** sample at Day 1 and a second sample at either Week 148 or at Withdrawal (if a subject is withdrawn prior to Week 148) will be taken for all subjects. **Additionally, where possible, stored whole blood from Day 1 will be used for telomere length evaluation (while telomere length evaluation at Week 96 and Week 144 require a separate whole blood sample).**
v. Whole blood samples for telomere length evaluation will be taken at Week 96 and Week 144 (where possible, the Day 1 evaluation will be done from the stored whole blood 'virology/telomere length' sample in footnote 'u').
w. At Screening, a subject number will be generated.

- **Section 7.4.5. Clinical Safety Laboratory Assessments, Table 1.**

Amended text:

Other Laboratory Tests	• Plasma HIV-1 RNA [6] • CD4+ cell counts • Hepatitis B (HBsAg, anti-HBc, anti-HBs, HBV DNA) • Hepatitis C (anti-HCV) • RPR • PT/INR • Serum hCG pregnancy test (as needed for females of reproductive potential) [7] • Urinalysis, urine albumin/creatinine ratio, and urine protein/creatinine ratio, urine phosphate • Renal biomarkers including Cystatin C (blood), Retinol Binding Protein (RBP, blood/urine); and Beta-2 Microglobulin (B2M, blood/urine) [8] • Bone biomarkers including: bone-specific alkaline phosphatase, procollagen type I N-terminal propeptide, type I collagen cross-linked C-telopeptide, osteocalcin, 25-hydroxyvitamin D [8] • **Inflammation biomarkers including IL-6 and hs-CRP [8]** • **Telomere length [8]**
ALT = alanine aminotransferase, anti-HBc = hepatitis B core antibody, anti-HBs = hepatitis B surface antibody, anti-HCV = hepatitis C antibody, AST = aspartate aminotransferase, BUN = blood urea nitrogen, CO_2 = carbon dioxide, HBsAg = hepatitis B surface antigen, HBV DNA = hepatitis B virus deoxyribonucleic acid, HDL = high density lipoprotein, LDL = low density lipoprotein, MCH = mean corpuscular haemoglobin, MCV = mean corpuscular volume, PT/INR = prothrombin time/international normalised ratio, RBC = red blood cells, RPR = rapid plasma reagin, WBC = white blood cells; **IL-6 = interleukin 6, hs-CRP = high-sensitivity C-reactive protein**	

- **Section 7.5. Biomarkers**

Amended text:

Blood and/**or** urine are being collected to perform **evaluations of** renal, ~~and~~ bone **and inflammation biomarkers, and telomere length** ~~biomarker assessments~~ as outlined in Section 7.1.

Renal biomarkers include:
- Cystatin C (blood)
- Retinol Binding Protein (RBP, blood/urine),
- Beta-2-Microglobulin (B2M, blood/urine),
- urine albumin/creatinine ratio,
- urine protein/creatinine ratio,
- urine phosphate, and
- serum creatinine.

Bone biomarkers (blood) include:
- bone-specific alkaline phosphatase,
- procollagen type 1 N-propeptide,
- type 1 collagen cross-linked C-telopeptide,
- osteocalcin, and
- 25-hydroxyvitamin D.

Inflammation biomarkers include:
- **interleukin-6 (IL-6, blood)**
- **high-sensitivity C reactive protein (hs-CRP, blood)**

Telomere length (whole blood)

- **Section 7.6.1. HIV-1 Exploratory Analyses**

Amended text:

Additional virologic analyses for HIV-1 may, for example, be carried out on ~~peripheral blood mononuclear cell (PBMC)~~ **whole blood** samples collected at Baseline or on study per Time and Events Table (Section 7.1), and/or on stored plasma samples from other relevant time points.

- **Section 11. References**

Amended text:

EPIVIR Product Information (lamivudine), September 201~~5~~**7**.

GlaxoSmithKline Document Number RM2007/00683/~~09~~**11**: GSK1349572 Clinical Investigator's Brochure, version ~~09~~**11**. October 201~~5~~**7**.

TIVICAY Product Information (dolutegravir), ~~August 2015~~**March 2017**

Truvada Product Information (emtricitabine/tenofovir disaproxil fumarate), ~~March 2016~~ **April 2017**

Additional Notes:

References to the Investigator's Brochure were updated in Section 2.1., Section 2.2., Section 4.6., Section 12.8.1.6., and Section 12.8. (References).

References to the product information for EPIVIR, TIVICAY and Truvada were updated in Section 2.1. and Section 6.7.

- **Section 11. References**

Additional text (references):

Cahn P, Rolón MJ, Figueroa MI, et al. Dolutegravir-lamivudine as initial therapy in HIV-Infected, ARV-naïve patients, 48 Week results of the PADDLE (Pilot Antiretroviral Design with Dolutegravir LamivudinE) study. J.Int AIDS Society 2017, 20:21678.

Leeansyah E, Cameron PU, Solomon A, et al. Inhibition of telomerase activity by human immunodeficiency virus (HIV) nucleos(t)ide reverse transcriptase inhibitors: a potential factor contributing to HIV-associated accelerated aging. J Infect Dis. 2013;207:1157–65.

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- **Section 12.1. Appendix 1: Abbreviations and Trademarks**

Additional text (abbreviations):

hs-CRP	High-sensitivity C-reactive protein
IL-6	Interleukin-6

- **Section 12.7.6. Evaluating AEs and SAEs**

Amended text:

Assessment of Intensity:
The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the ~~following~~ categories **in the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE Grading Table") in Appendix 6, Section 12.6.:** • **Grade 1** / Mild: ~~An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.~~ • **Grade 2** / Moderate~~: An event that is sufficiently discomforting to interfere with normal everyday activities~~ • **Grade 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 utilised for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.~~ • **Grade 4 / Potentially life threatening** • **Grade 5 / Death** • 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.

- **Section 12.8.1.4. Proteinuria**

Amended text:

Subjects with an abnormal urine ~~micro~~albumin/creatinine ratio (>0.3 mg/mg, >300 mg/g, or >34 mg/mmol) that represents a change from Baseline and no associated increase in creatinine, should have a repeat spot urine ~~micro~~albumin/creatinine ratio performed within 2-4 weeks. If confirmed, then consideration should be given to additional evaluation after consultation with the study Medical Monitor. Additional evaluation may include a 24-hour urine protein and creatinine measurement and nephrology referral.

- **Section 12.9.1. Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)**

Additional text (i.e., an additional method was added to the list of methods for avoiding pregnancy):

In addition, male condom combined with a vaginal spermicide (foam, gel, film, cream, or suppository) [Hatcher, 2011] is included in this study as a permitted method of contraception.

- **Section 12.9.2. Collection of Pregnancy Information**

Additional text:

- **GSK's central safety department will also 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/.**

TITLE PAGE

Division: Worldwide Development

Information Type: Clinical Protocol

Title:	A Phase III, randomised, double-blind, multicentre, parallel-group, non-inferiority study evaluating the efficacy, safety, and tolerability of dolutegravir plus lamivudine compared to dolutegravir plus tenofovir/emtricitabine in HIV-1-infected treatment-naïve adults

Compound Number: GSK1349572 + GR109714 (GSK3515864)

Development Phase III

Effective Date: 25-APR-2016

Author(s): PPD

SPONSOR SIGNATORY:

PPD

4/25/16

Kimberly Y. PPD th, PPD PH
Vice Presiden[redacted]cal Strategy,
ViiV Healthcare

Date

PPD

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Site Address
Primary Medical Monitor	PPD MD	PPD		ViiV Healthcare 5 Moore Drive Research Triangle Park, NC 27709 (USA)
Secondary Medical Monitor	PPD MD			ViiV Healthcare Mailstop UP4410 Collegeville, PA (USA)
SAE contact information	Medical Monitor as above			

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

Global Sponsor Legal Registered Address (excluding US):

ViiV Healthcare UK Limited
980 Great West Road
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UK

US IND Sponsor Legal Registered Address:

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Five Moore Drive
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Research Triangle Park, NC 27709-3398, USA
Telephone: PPD

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 VP, Global Medical Strategy.

Regulatory Agency Identifying Number(s): US IND 75,382; EudraCT 2015-004418-95

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For Protocol Number 204861:

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name: _____

_____ _____

Investigator Signature Date

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1. PROTOCOL SYNOPSIS FOR STUDY 204861

Rationale

Study 204861 is being conducted to compare a simplified two-drug regimen of dolutegravir (DTG) plus lamivudine (3TC) with a standard three-drug first-line regimen in human immunodeficiency virus type 1 (HIV-1) infected, antiretroviral therapy (ART)-naïve adult subjects. The study is designed to demonstrate the non-inferior antiviral activity of DTG plus 3TC once daily compared to DTG plus tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) fixed-dose combination (FDC) once daily at 48 weeks. This study will also characterise the long-term antiviral activity, tolerability and safety of DTG plus 3TC through Week 148.

An identical sister study, 205543, will be conducted in parallel with Study 204861 in some countries. The clinical development programme of DTG plus 3TC aims to develop a FDC tablet of these products.

Objectives/Endpoints

Objectives	Endpoints
Primary	
• To demonstrate non-inferior antiviral activity of DTG + 3TC versus DTG + TDF/FTC at 48 weeks in HIV-1-infected, ART-naïve subjects	• Proportion of subjects with plasma HIV-1 RNA <50 copies/mL (c/mL) at Week 48 using the FDA Snapshot algorithm [Missing, Switch or Discontinuation = Failure (MSD=F)] for the intent-to-treat exposed (ITT-E) population
Secondary	
• To demonstrate the antiviral activity of DTG + 3TC versus DTG + TDF/FTC at 24, 96 and 144 weeks	• Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Weeks 24, 96 and 144 using the FDA Snapshot algorithm (MSD=F) for the ITT-E population
• To evaluate the antiviral activity, immunological effects, and incidence of disease progression (HIV-associated conditions, AIDS and death) of DTG + 3TC compared to DTG + TDF/FTC over time	• Time to viral suppression (HIV-1 RNA <50 c/mL); • Absolute values and changes from Baseline in CD4+ cell counts at Weeks 24, 48, 96 and 144; • Incidence of disease progression (HIV-associated conditions, AIDS and death).
• To assess viral resistance in subjects meeting confirmed virologic withdrawal (CVW) criteria	• Incidence of treatment-emergent genotypic and phenotypic resistance to DTG and 3TC or TDF/FTC in subjects meeting CVW criteria
• To evaluate the safety and tolerability of DTG + 3TC compared to DTG + TDF/FTC over time	• Incidence and severity of adverse events (AEs) and laboratory abnormalities; • Proportion of subjects who discontinue treatment due to AEs over 24, 48, 96 and

Objectives	Endpoints
	144 weeks
• To evaluate renal biomarkers (in urine and blood) and bone biomarkers (in blood) in subjects treated with DTG + 3TC compared to DTG + TDF/FTC	• Change from Baseline in renal and bone biomarkers at Weeks 24, 48, 96 and 144
• To evaluate the effects of DTG + 3TC on fasting lipids compared to DTG + TDF/FTC over time	• Change from Baseline in fasting lipids at Weeks 24, 48, 96, and 144; • The incidence of Grade 2 or greater laboratory abnormalities in fasting LDL cholesterol by Weeks 24, 48, 96, and 144;
• To evaluate the effect of patient demographics and baseline characteristics (e.g. demographic factors, HIV-1 subtype, baseline CD4+ cell count) on response to DTG + 3TC compared to DTG + TDF/FTC over time	• Proportion of subjects by patient subgroup(s) (e.g. by age, gender, Baseline CD4+ cell count) with plasma HIV-1 RNA <50 c/mL at Weeks 24, 48, 96 and 144 using the Snapshot algorithm for the ITT-E population • Change from Baseline in CD4+ cell counts at Weeks 24, 48, 96 and 144 by patient subgroups
• To assess change in health-related quality-of-life for subjects treated with DTG plus 3TC compared to DTG + TDF/FTC	• Change from Baseline in health related quality of life using EQ-5D-5L at Weeks 4, 24, 48, 96, and 144 (or Withdrawal from the study)

Overall Design

This study is a Phase III, randomised, double-blind, active-controlled, multicentre, parallel-group, non-inferiority study. The study will enrol approximately 700 HIV-1 infected, ART-naïve subjects with a Screening HIV-1 RNA of 1000 to ≤500,000 copies/mL (c/mL). Subjects will be randomised 1:1 to receive a two-drug regimen of DTG plus 3TC once daily (approximately 350 subjects) or DTG plus the FDC tablet of TDF/FTC once daily (approximately 350 subjects) until Week 148. Subjects will be stratified by screening HIV-1 RNA (≤100,000 c/mL or >100,000 c/mL) and Screening CD4+ cell count (≤ or >200 cells/mm^3).

The study initially will enrol approximately 100 subjects with a Screening HIV-1 RNA of 1000 to ≤100,000 c/mL. Accumulated data from other clinical trials investigating the DTG plus 3TC dual regimen will undergo independent review. If the independent review is supportive of evaluating the dual regimen's efficacy in subjects with a Screening viral load of up to 500,000 c/mL, recruitment will be opened to subjects with a Screening HIV-1 RNA of 1000 to ≤500,000 c/mL. If the review does not support enrolment of such subjects, the Screening viral load will remain capped at ≤100,000 c/mL.

Treatment Arms and Duration

The study will comprise a 28-day Screening Phase (which may be extended to 35 days to allow receipt of all Screening assessment results), a Double-blind Randomised Phase

(Day 1 to Week 96), and an Open-label Randomised Phase (Week 96 to Week 148). If required by local regulations, subjects randomised to receive DTG plus 3TC once daily who successfully complete 148 weeks of treatment will continue to have access to DTG plus 3TC once daily (Continuation Phase) until (i) 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 (ii) the DTG/3TC FDC tablet, if required by local regulations, is available, or (iii) the subject no longer derives clinical benefit, or (iv) the subject meets a protocol-defined reason for discontinuation, or (v) development of the DTG plus 3TC dual regimen is terminated. Subjects randomised to the DTG plus TDF/FTC FDC arm will receive DTG plus TDF/FTC FDC through their Week 148 visit only, after which subjects will complete the study and will need to have alternate arrangements in place to access antiretroviral medication. No dose reductions, modifications in dosage, or changes in the frequency of dosing will be allowed in this study.

At Weeks 28, 52, 100, and 148, a confirmatory viral load measurement will be performed for subjects presenting with HIV-1 RNA ≥50 c/mL at the Week 24, 48, 96 and 144 visits, respectively. The primary and secondary efficacy endpoints correspond to viral load measurements collected within a ≤6 week window around the visits of interest (including data from the visits at Weeks 28, 52, 100, and 148), as per the FDA's Snapshot algorithm. For this reason, the primary and secondary analyses are denoted as occurring at Weeks 24, 48, 96 and 144 with the understanding that respective data from the Week 28, 52, 100 and 148 visits may be included.

An Independent Data Monitoring Committee (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 and sister study 205543.

Type and Number of Subjects

The study will be conducted in approximately 700 HIV-1 infected, ART-naïve adults with a Screening HIV RNA of 1000 to ≤500,000 c/mL. Approximately 950 subjects will be screened such that approximately 700 subjects are enrolled into the study.

Analysis

The primary analysis at Week 48 will take place after the last subject has had their Week 48 viral load assessed, including a retest if required. The primary analysis method for the proportion of responders at Week 48 will be a Cochran-Mantel-Haenszel test stratified by Baseline plasma HIV-1 RNA (≤ vs. >100,000 c/mL) and Baseline CD4+ cell count (≤ vs. >200 cells/mm^3).

Assuming a true 87% response rate in the DTG plus 3TC arm and an 89% response rate in the DTG plus TDF/FTC FDC arm at Week 48, a non-inferiority margin of -10%, and a 2.5% one-sided significance level, this study requires 347 subjects per treatment arm. This would provide 90% power to show non-inferiority for the proportion of subjects with plasma HIV-1 RNA <50 c/mL at 48 weeks. If we observed an 89% response rate

for the DTG plus TDF/FTC FDC arm, non-inferiority would be declared if the observed treatment difference was better than -4.8 percentage points.

2. INTRODUCTION

2.1. 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 [BHIVA, 2015; DHHS, 2016; EACS, 2015; IAS-USA, 2014]. While these regimens are highly efficacious and generally well tolerated, there is growing concern about long-term toxicities, and great interest from patients and clinicians in unique regimens that might avoid such toxicities, and to provide effective long-term ART with the most streamlined regimens possible.

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, 2015; GlaxoSmithKline Document Number RM2007/00683/09].

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™) [EPIVIR Package Insert, 2015], it is also available as part of two backbone FDC products (zidovudine (ZDV)/3TC, COMBIVIR™ and abacavir (ABC)/3TC, EPZICOM™/KIVEXA™). 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 [GlaxoSmithKline Document Number RM2007/00683/09; Walmsley, 2013].

DTG plus 3TC may provide 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 could be 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).

Study 204861 compares a simplified two-drug regimen of DTG plus 3TC once daily with one of the preferred first line three-drug regimens consisting of DTG plus two NRTIs (TDF/FTC FDC) once daily [BHIVA, 2015; DHHS, 2016; EACS, 2015; IAS-USA, 2014] in HIV-1-infected, ART-naïve subjects. Initially, it will enrol subjects with a

Screening HIV 1 RNA of 1000 to ≤100,000 c/mL, but recruitment may later be opened to subjects with a Screening HIV-1 RNA of 1000 to ≤500,000 c/mL. The selection of 500,000 c/mL as the Screening viral load cap is reasonable based on the response rates previously observed during short-term monotherapy with DTG and for 3TC. In the DTG Phase IIa dose-ranging study, subjects receiving monotherapy of DTG 50 mg once daily had a 2.5 log10 decline in HIV-1 RNA after 10 days of treatment [Min, 2011]. In early studies of HIV treatments, in which subjects were given 3TC monotherapy, a 1.5 log10 decline in HIV-1 RNA was observed over 2 weeks [Eron, 1995; Kuritzkes, 1996]. Thus, based on these levels of response, a 4 log10 decline in HIV-1 RNA could perhaps be achieved due to the combined activity of the two components. Starting with a viral load of 500,000 c/mL (5.7 log10 c/mL), a 4 log10 decline would result in HIV-1 RNA levels approximately at or less than 50 c/mL (1.7 log10 c/mL).

An identical sister study, 205543, will be conducted in parallel with Study 204861 in some countries. The overall objective of the clinical development program of DTG plus 3TC is to develop a FDC tablet.

2.2. Brief Background

A number of clinical studies have been published to date that provide supportive clinical data on the efficacy as well as favourable safety of two-drug first-line treatment regimens 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 subjects are extensive, with no resistance mutations being identified through 144 weeks of treatment (SINGLE, ING114467) [Walmsley, 2015; GlaxoSmithKline Document Number RM2007/00683/09]. 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.

Three randomised 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 enrol 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 [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 subjects 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].

An ongoing investigator-initiated 48-week pilot study, the PADDLE trial (NCT02211482), is being conducted in 20 HIV treatment-naïve subjects with no genotypic resistance to 3TC and a viral load of ≤100,000 c/mL at Screening and has provided notable early data on the efficacy of a once-daily DTG plus 3TC two-drug regimen. Subjects 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. By Week 8, all 20 subjects, including 4 subjects with a Baseline HIV-1 RNA of >100,000 c/mL, had reached a viral load of <50 c/mL and all maintained virologic suppression through Week 24 [Figueroa, 2015].

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To demonstrate non-inferior antiviral activity of DTG + 3TC versus DTG + TDF/FTC at 48 weeks in HIV-1-infected, ART-naïve subjects	• Proportion of subjects with plasma HIV-1 RNA <50 copies/mL (c/mL) at Week 48 using the FDA Snapshot algorithm [Missing, Switch or Discontinuation = Failure (MSD=F)] for the intent-to-treat exposed (ITT-E) population
Secondary	
• To demonstrate the antiviral activity of DTG + 3TC versus DTG + TDF/FTC at 24, 96 and 144 weeks	• Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Weeks 24, 96 and 144 using the FDA Snapshot algorithm (MSD=F) for the ITT-E population
• To evaluate the antiviral activity, immunological effects, and incidence of disease progression (HIV-associated conditions, AIDS and death) of DTG + 3TC compared to DTG + TDF/FTC over time	• Time to viral suppression (HIV-1 RNA <50 c/mL); • Absolute values and changes from Baseline in CD4+ cell counts at Weeks 24, 48, 96 and 144; • Incidence of disease progression (HIV-associated conditions, AIDS and death).

Objectives	Endpoints
• To assess viral resistance in subjects meeting confirmed virologic withdrawal (CVW) criteria	• Incidence of treatment-emergent genotypic and phenotypic resistance to DTG and 3TC or TDF/FTC in subjects meeting CVW criteria
• To evaluate the safety and tolerability of DTG + 3TC compared to DTG + TDF/FTC over time	• Incidence and severity of adverse events (AEs) and laboratory abnormalities; • Proportion of subjects who discontinue treatment due to AEs over 24, 48, 96 and 144 weeks
• To evaluate renal biomarkers (in urine and blood) and bone biomarkers (in blood) in subjects treated with DTG + 3TC compared to DTG + TDF/FTC	• Change from Baseline in renal and bone biomarkers at Weeks 24, 48, 96 and 144
• To evaluate the effects of DTG + 3TC on fasting lipids compared to DTG + TDF/FTC over time	• Change from Baseline in fasting lipids at Weeks 24, 48, 96, and 144; • The incidence of Grade 2 or greater laboratory abnormalities in fasting LDL cholesterol by Weeks 24, 48, 96, and 144;
• To evaluate the effect of patient demographics and baseline characteristics (e.g. demographic factors, HIV-1 subtype, baseline CD4+ cell count) on response to DTG + 3TC compared to DTG + TDF/FTC over time	• Proportion of subjects by patient subgroup(s) (e.g. by age, gender, Baseline CD4+ cell count) with plasma HIV-1 RNA <50 c/mL at Weeks 24, 48, 96 and 144 using the Snapshot algorithm for the ITT-E population • Change from Baseline in CD4+ cell counts at Weeks 24, 48, 96 and 144 by patient subgroups
• To assess change in health-related quality-of-life for subjects treated with DTG plus 3TC compared to DTG + TDF/FTC	• Change from Baseline in health related quality of life using EQ-5D-5L at Weeks 4, 24, 48, 96, and 144 (or Withdrawal from the study)

4. STUDY DESIGN

4.1. Overall Design

This study is a Phase III, randomised, double-blind, active-controlled, multicentre, parallel-group, non-inferiority study. The study will be conducted in approximately 700 HIV-1 infected, ART-naïve subjects with a Screening HIV-1 RNA of 1000 to ≤500,000 copies/mL (c/mL). Subjects will be randomised 1:1 to receive a two-drug regimen of DTG plus 3TC once daily (approximately 350 subjects) or DTG plus the FDC tablet of TDF/FTC once daily (approximately 350 subjects). Subjects will be stratified by screening HIV-1 RNA (≤100,000 c/mL or >100,000 c/mL) and Screening CD4+ cell count (≤ or >200 cells/mm^3).

The study initially will enrol approximately 100 subjects with a Screening HIV-1 RNA of 1000 to ≤100,000 c/mL. Accumulated data from other clinical trials investigating the DTG plus 3TC dual regimen will undergo independent review. If the independent review is supportive of evaluating the dual regimen's efficacy in subjects with a Screening viral load of up to 500,000 c/mL, recruitment will be opened to subjects with a Screening HIV-1 RNA of 1000 to ≤500,000 c/mL. If the review does not support enrolment of such subjects, the Screening viral load will remain capped at ≤100,000 c/mL.

The study will comprise:

- a 28-day Screening Phase (which may be extended to 35 days to allow receipt of all Screening assessment results),
- a Double-blind Randomised Phase (Day 1 to Week 96),
- an Open-label Randomised Phase (Week 96 to Week 148), and
- a Continuation Phase (Figure 1).

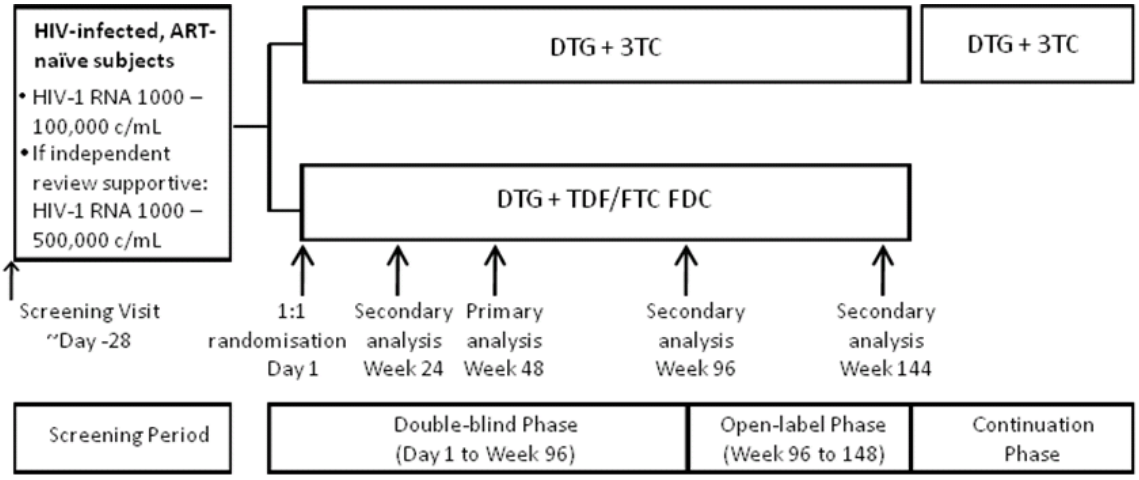
All subjects who successfully complete 96 weeks of randomised, blinded treatment will continue to receive their randomised treatment (DTG plus 3TC or DTG plus TDF/FTC FDC) in an open-label manner as part of the study through Week 148. Data from these subjects will provide long-term, comparative, descriptive information on durability of response, safety, and tolerability.

Subjects randomised to receive DTG plus 3TC who successfully complete 148 weeks of treatment may continue to have access to DTG plus 3TC in a Continuation Phase.

At Weeks 28, 52, 100, and 148, a confirmatory viral load measurement will be performed for subjects presenting with HIV-1 RNA ≥50 c/mL at the Week 24, 48, 96 and 144 visits, respectively. The primary and secondary efficacy endpoints correspond to viral load measurements collected within a ≤6 week window around the visits of interest (including data from the visits at Weeks 28, 52, 100, and 148), as per the FDA's Snapshot algorithm. For this reason, the primary and secondary analyses are denoted as occurring at Weeks 24, 48, 96 and 144 with the understanding that respective data from the Week 28, 52, 100 and 148 visits may be included.

Assuming a true response rate of 87% for the DTG plus 3TC arm and an 89% response rate for the DTG plus TDF/FTC arm at Week 48, the study requires 347 subjects per arm to have 90% power with a 10% non-inferiority margin and a 2.5% one-sided alpha level.

Figure 1 204861 Study Schematic



4.2. Treatment Arms and Duration

The study will be conducted in approximately 700 HIV-1 infected, ART-naïve individuals. Eligible subjects will be randomised 1:1 to receive DTG plus 3TC once daily or DTG plus TDF/FTC FDC once daily.

No dose reductions, modifications in dosage, or changes in the frequency of dosing will be allowed in this study, except those allowed and defined in the protocol.

The study will include a 28-day Screening Phase (which may be extended to 35 days to allow receipt of all Screening assessment results), a Double-blind Randomised Phase (Day 1 to Week 96), an Open-label Randomised Phase (Week 96 to Week 148), and a Continuation Phase (post-Week 148).

If required by local regulations, subjects randomised to receive DTG plus 3TC once daily who successfully complete 148 weeks of treatment will continue to have access to DTG plus 3TC once daily in a 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 available, or
- the subject no longer derives clinical benefit, or
- the subject meets a protocol-defined reason for discontinuation, or
- development of the DTG plus 3TC dual regimen is terminated.

Subjects randomised to the DTG plus TDF/FTC FDC arm will receive DTG + TDF/FTC FDC through their Week 148 visit only, after which subjects will complete the study and will need to have alternate arrangements in place to access antiretroviral medication.

Subjects with ongoing AEs or laboratory abnormalities considered to be AEs will attend a Follow-up visit approximately four weeks after their last dose of study treatment.

Assessments at the Follow-up visit should reflect any ongoing complaints (e.g. blood draws to follow a laboratory abnormality). The Follow-Up visit is not required for successful completion of the study.

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 and sister study 205543. 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. Further, an interim futility analysis will be performed for the IDMC to evaluate the efficacy and safety of DTG plus 3TC when approximately 50% of subjects have completed their visit at Week 24; the sponsor will remain blinded to this analysis. Full details of the methods, timing, decision criteria and operating characteristics will be pre-specified in the IDMC Charter.

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

4.3. Type and Number of Subjects

Assuming a 26% screen failure rate, approximately 950 HIV-1-infected adult subjects will be screened to achieve approximately 700 randomised subjects to include approximately 350 subjects per treatment group.

The study initially will enrol approximately 100 subjects with a Screening HIV-1 RNA of 1000 to ≤100,000 c/mL. Accumulated data from other clinical trials investigating the DTG plus 3TC dual regimen will undergo independent review. If the independent review is supportive of evaluating the dual regimen's efficacy in subjects with a Screening viral load of up to 500,000 c/mL, recruitment will be opened to subjects with a Screening HIV-1 RNA of 1000 to ≤500,000 c/mL. If the review does not support enrolment of such subjects, the Screening viral load will remain capped at ≤100,000 c/mL.

A goal of this study is to target populations who are underrepresented in clinical studies, including approximately 15% women and approximately 15% subjects aged 50 years or older.

4.4. Design Justification

The use of randomised, active-controlled, double-blind, multicentre, parallel group, fully-powered non-inferiority studies as pivotal proof of safety and efficacy is a well established experimental design for establishing the non-inferiority of an investigational agent or regimen compared to an active comparator and is generally accepted at regulatory authorities as rigorous proof of antiviral activity [CDER, 2015]. The primary endpoint, proportion of subjects at Week 48 with plasma HIV-1 RNA below the assay limit of detection (e.g. <50 c/mL), is also a very well-established surrogate endpoint for prognosis of HIV-1 infection and disease progression [CDER, 2015].

A number of clinical studies to date have provided supportive clinical data on the efficacy as well as favourable safety of two-drug first-line treatment regimens that include a boosted PI or an INSTI (see Section 2.2).

The comparator regimen, DTG plus TDF/FTC, has been established as one of the preferred first-line treatment regimens for treatment-naïve HIV infected subjects and is recognised as such, as evidenced by its wide acceptance in treatment guidelines [BHIVA, 2015; DHHS, 2016; EACS, 2015; IAS-USA, 2014].

Considering these points above, the proposed study design should allow a thorough assessment of the DTG plus 3TC regimen.

4.5. Dose Justification

The efficacy, PK, safety, and drug interaction potential of DTG, 3TC, TDF and FTC as individual agents and of TDF/FTC FDC have been evaluated in extensive clinical development programmes. DTG, 3TC and TDF/FTC FDC are approved and marketed as TIVICAY 50 mg once daily, EPIVIR 300 mg once daily, and Truvada 300 mg/200 mg once daily respectively, the doses used in the current study.

4.6. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with DTG and 3TC can be found in the DTG Investigator's Brochure (IB) [GlaxoSmithKline Document Number RM2007/00683/09] and DTG and 3TC product labels. The following section outlines the risk assessment and mitigation strategy primarily for DTG in this protocol. For 3TC and TDF/FTC, the approved country product labels should be referenced. The comparator regimen, DTG plus TDF/FTC, has been established as a preferred first line treatment regimen for treatment-naïve HIV infected subjects and is recognised as such, as evidenced by it wide acceptance in treatment guidelines [BHIVA, 2015; DHHS; 2016; EACS, 2015; IAS-USA, 2014].

4.6.1. Risk Assessment

The following table outlines the risk assessment and mitigation strategy for this protocol.

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy[a]
Investigational Product (IP) [DTG, 3TC, TDF/ FTC] Refer to DTG IB and country product labels 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.	Subjects with history of allergy/sensitivity to any of the study drugs are excluded (Section 5.2). Specific/detailed toxicity management guidance is provided for HSR (Section 12.8.1.5) and rash (Section 12.8.1.6). The subject informed consent form includes information on this risk and the actions subjects 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, subjects 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	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 subjects 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 subjects, likely contributed to significant elevations in liver chemistries. Current treatment guidelines [DHHS, 2016; EACS, 2015] do not recommend monotherapy with 3TC for patients with HBV infection, which is what subjects randomised to DTG plus 3TC, would effectively be receiving. Emergence of	Subjects meeting either of the following criteria during the screening period are excluded from participating (Section 5.2). • Alanine aminotransferase (ALT) ≥5 times the upper limit of normal (ULN) or ALT ≥3x ULN and bilirubin ≥1.5x ULN (with >35% direct bilirubin); • Subjects positive for Hepatitis B surface antigen (HBsAg); subjects 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; • Subjects 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

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy[a]
Investigational Product (IP) [DTG, 3TC, TDF/ FTC] Refer to DTG IB and country product labels for additional information		
	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 subjects can result in severe exacerbations of hepatitis B.	drug:drug interactions with study treatment throughout the entire study period. Specific/detailed liver stopping criteria and toxicity management guidance is provided for suspected DILI or other clinically significant liver chemistry elevations (Appendix 3, Section 12.3).
DTG: Psychiatric disorders	Psychiatric disorders including suicidal ideation and behaviours are common in HIV-infected patients. The psychiatric profile for DTG (including suicidality, depression, bipolar and hypomania, anxiety and abnormal dreams) was similar to RAL- or favourable 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.	Subjects who in the investigator's judgment, pose a significant suicidality risk, are excluded from participating (Section 5.2). 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 subjects who experience signs of suicidal ideation or behaviour (Section 7.4.6). The subject informed consent form includes information on this risk of depression and suicidal ideation and behaviours.

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy[a]
Investigational Product (IP) [DTG, 3TC, TDF/ FTC] Refer to DTG IB and country product labels for additional information		
DTG and 3TC: Increased rates of virologic failure/ observed resistance	Lower responses in subjects 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]. 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 subjects. 3TC: M184V is a common single mutation that leads to full resistance to 3TC.	Subjects with evidence of primary viral resistance based on the presence of any major resistance-associated mutation (including M184V) are excluded from this study (Section 5.2). The study will initially enrol subjects with a Screening HIV 1 RNA of 1000 to ≤100,000 c/mL. Following an independent review of clinical data on the DTG plus 3TC treatment regimen, the Screening viral load cap may be increased to 500,000 c/mL. The viral load cap will maximise the opportunity for subjects randomised to the DTG plus 3TC arm to rapidly achieve an undetectable viral load (HIV-1 RNA <50 c/mL), which may help minimise the potential for emergent drug resistance that could result in functional DTG monotherapy (i.e. if the M184V mutation arises, conferring 3TC resistance). Subjects will have HIV-1 RNA measured at each study visit. An IDMC will be instituted to ensure external objective medical and/or statistical review of efficacy and safety (Section 10.8). 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 9.3.4).
DTG: Theoretical serious drug interaction with dofetilide and pilsicainide	Co-administration of DTG may increase dofetilide/pilsicainide plasma concentration via inhibition of organic cation transporter 2 (OCT2), resulting in potentially life-threatening toxicity.	The co-administration of DTG with dofetilide or pilsicainide is prohibited in the study (Section 6.9.2).
DTG, 3TC, and TDF/FTC: 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, TDF and FTC are eliminated by renal excretion and exposures increase in patients with renal dysfunction. Renal failure, renal impairment, elevated creatinine, hypophosphataemia and proximal tubulopathy (including Fanconi syndrome) have been reported with the use of TDF in clinical practice.	Due to requirements for dose reduction of 3TC or dose interval adjustments of TDF/FTC in patients with renal dysfunction, subjects with a creatinine clearance (CrCL) <50 mL/min/1.73 m^2 are excluded (Section 5.2). CrCl is calculated in all patients prior to initiating therapy and renal function (creatinine clearance and serum phosphate) will be monitored at all subsequent study visits.

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy[a]
Investigational Product (IP) [DTG, 3TC, TDF/ FTC] Refer to DTG IB and country product labels for additional information		
		Specific/detailed toxicity management guidance is provided for subjects who develop a decline in renal function/proximal renal tubule dysfunction (PRTD) (Section 12.8.1.3) or proteinuria (Section 12.8.1.4).
DTG: Creatine Phosphokinase (CPK) elevations	Asymptomatic CPK elevations mainly in association with exercise have been reported with DTG therapy.	Specific detailed toxicity management guidance is provided for subjects who develop Grade 3 to 4 CPK elevations (Section 12.8.1.8).

a. Careful monitoring of events will be conducted using serious adverse event (SAE) reports and alerts for Grade 3/4 laboratory toxicities (per Division of Acquired Immune Deficiency Syndrome [DAIDS] toxicity gradings for HIV-infected patients). Serious/severe events will be managed appropriately including, but not limited to, withdrawal of study drug, and will be followed to resolution as per Sponsor's standard medical monitoring practices.
Clinical Safety Data will be routinely reviewed in GlaxoSmithKline (GSK) Safety Review Team meetings. This will include in-stream review of data from this clinical trial on a routine basis, review of aggregate data on a protocol and program basis when available, and review of competitor data from the literature.

4.6.2. 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 ART agents. DTG 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 2.2). Results from these trials pave the way for the exploration of other dual-therapy strategies, such as DTG plus 3TC, a regimen of two well-characterised antiretrovirals that may provide 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.

4.6.3. Overall Benefit:Risk Conclusion

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

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the ViiV Healthcare investigational product or other study treatment that may impact subject eligibility is provided in the DTG IB and the respective product labels.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardise the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

Subjects are allowed to re-screen for this study one time, except where exclusionary HIV-1 resistance was present; re-screening will require a new subject 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 following are study specific eligibility criteria unless stated otherwise. In addition to these criteria, Investigators must exercise clinical discretion regarding selection of

appropriate study subjects, taking into consideration any local treatment practices or guidelines and good clinical practice (GCP).

5.1. Inclusion Criteria

Eligible subjects 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. no active substance abuse, acute major organ disease, or planned long-term work assignments out of the country).

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

AGE
1. HIV-1 infected adults ≥18 years of age (or older, if required by local regulations), at the time of signing the informed consent.

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Screening plasma HIV-1 RNA of 1000 c/mL to ≤100,000 c/mL. If an independent review of accumulated data from other clinical trials investigating the DTG plus 3TC dual regimen is supportive of the DTG plus 3TC treatment regimen, enrolment will be opened to subjects with Screening plasma HIV-1 RNA of 1000 c/mL to ≤500,000 c/mL; 3. Antiretroviral-naïve (defined as ≤10 days of prior therapy with any antiretroviral agent following a diagnosis of HIV-1 infection). Subjects 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 >1 year from HIV diagnosis or there is documented HIV seronegativity between the last prophylactic dose and the date of HIV diagnosis.

SEX
4. Male or female. A female subject 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 test at Baseline), not lactating, and at least one of the following conditions applies: a. Non-reproductive potential defined as: • Pre-menopausal females with one of the following:

- Documented tubal ligation
- Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
- Hysterectomy
- Documented Bilateral Oophorectomy

- Postmenopausal defined as 12 months of spontaneous amenorrhea and ≥45 years of age [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and oestradiol levels consistent with menopause is confirmatory (refer to laboratory reference ranges for confirmatory levels)]. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment.

b. Reproductive potential and agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see Appendix 9, Section 12.9.1) from 30 days prior to the first dose of study medication and until the last dose of study medication and completion of the Follow-up visit.

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

All subjects 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
5. Subject or the subject's legal representative capable of giving signed informed consent as described in Section 10.2 which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

OTHER
6. **Subjects enrolled in France**: A subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

CONCURRENT CONDITIONS/MEDICAL HISTORY
1. Women 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 disease [CDC, 2014], except cutaneous Kaposi's sarcoma not requiring systemic therapy and historical or current CD4 cell counts less than 200 cells/mm^3. 3. Subjects with severe hepatic impairment (Class C) as determined by Child-Pugh classification (Appendix 2, 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: • Subjects positive for HBsAg are excluded; • Subjects negative for anti-HBs but positive for anti-HBc (negative HBsAg status) and positive for HBV DNA are excluded. NOTE: Subjects 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. 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). Subjects who are at least 14 days post completed treatment are eligible. 8. History or presence of allergy or intolerance to the study drugs or their components or drugs of their class; 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 localised malignancies require agreement between the investigator and the Study Medical Monitor for inclusion of the subject. 10. Subjects who in the investigator's judgment, poses a significant suicidality risk. Recent history of suicidal behaviour 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, except recognised ART as allowed above (inclusion criterion 3.), with documented activity against HIV-1 *in vitro* within 28 days of first dose of study treatment; 14. 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. 15. **Subjects enrolled in France**: the subject has participated in any study using an investigational drug during the previous 60 days or 5 half-lives, or twice the duration of the biological effect of the experimental drug or vaccine, whichever is longer, prior to screening for the study or the subject will participate simultaneously in another clinical study.

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 [IAS-USA, 2014] 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 subject'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 via the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) method.

5.3. Screening Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomised. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events (see Section 7.4.1.6).

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

5.4. Withdrawal/Stopping Criteria

Subjects permanently discontinuing study treatments prior to Week 148 are considered to be withdrawn from the study treatments and also from the study.

A subject 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 subject 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 subjects will not be replaced.

Subjects 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 subjects who withdraw from the study.

Subjects 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.

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

- Subject or Investigator non-compliance;
- At the request of the subject, Investigator, GSK or ViiV Healthcare;
- The subject requires concurrent prohibited medications during the course of the study. The subject 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 subject.

Subjects <u>must</u> be discontinued from the study for any of the following reasons:

- CVW criteria as specified in Section 5.4.1.3 are met;
- Subject requires substitution or dose modification of DTG, 3TC, TDF or FTC;
- Liver toxicity where stopping criteria specified in Section 5.4.2 and Appendix 3, Section 12.3 are met and no compelling alternate cause is identified;
- Renal toxicity criteria as specified in Appendix 8, Section 12.8.1.3 are met and no compelling alternate cause is identified;
- Grade 4 clinical AE considered causally related to study drug (Appendix 8, Section 12.8.1);
- Allergic reaction or rash criteria as specified in Appendix 8 (Section 12.8.1.5 and Section 12.8.1.6, respectively) are met and no compelling alternate cause is identified;
- Pregnancy (intrauterine), regardless of termination status of pregnancy (Section 7.4.2).

If a subject is prematurely or permanently withdrawn from the study, the procedures described in the Time and Events Table (Section 7.1) for the Withdrawal visit – and if necessary the Follow Up visit – are to be performed.

A Follow-up visit may occur approximately 4 weeks after the last dose of study treatment and is only required in subjects with ongoing clinical or laboratory AEs at the time of Withdrawal. All data from the Withdrawal visit will be recorded, as they comprise an essential evaluation that should be done prior to discharging any subject from the study.

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

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

5.4.1. Virologic Criteria for Subject 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 in Section 5.4.1.1 wherein the virologic withdrawal criteria revolve around the HIV-1 RNA cut-off of 200 c/mL.

5.4.1.1. Virologic Withdrawal Criteria

Suspected Virologic Withdrawal criteria

A single HIV-1 RNA value as defined by Virologic Non-response or Virologic Rebound 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 two and four weeks after the subject met a SVW criterion unless a delay is necessary to meet the requirements of

confirmatory HIV-1 RNA testing as described in Section 5.4.1.2. 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 $\log_{10}$ c/mL by Week 12, with subsequent confirmation, unless plasma HIV-1 RNA is <200 c/mL.
- Confirmed plasma HIV-1 RNA levels ≥200 c/mL on 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.

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

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

5.4.1.2. Managing Subjects 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 subject's HIV-1 RNA plasma level qualifies him/her as meeting an SVW criterion, the Investigator should query the subject 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 two 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 subject should receive full doses of all study drugs.
- Confirmatory testing should be scheduled at least 4 weeks following any immunisation, during which time the subject should receive full doses of study drugs.
- If therapy is interrupted due to toxicity management, non-compliance, or other reasons, confirmatory testing should be scheduled 2 to 4 weeks following resumption of full doses of study drugs.

- The subject 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 subjects, whenever necessary.

5.4.1.3. Managing Subjects Meeting Confirmed Virologic Withdrawal Criteria

Once a subject has been confirmed as meeting a virologic withdrawal criterion, a '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.

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

The protease (PRO)/reverse transcriptase (RT)/integrase assays used in this study are not validated for plasma HIV-1 RNA levels <500 c/mL. Nevertheless, for all subjects who meet CVW Criteria, additional plasma samples will be analysed in an attempt to obtain genotype/phenotype data on as many samples as possible. Subjects 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 subjects.

If a subject 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 7.1). These data will be recorded, as they comprise an essential evaluation that needs to be done before discharging any subject from the study.

5.4.1.4. Managing subjects with HIV-1 RNA ≥ 50 c/mL at Weeks 24, 48, 96 and 144

At Weeks 24, 48, 96 and 144 (key study endpoint visits) repeat HIV-1 RNA testing is required for any HIV-1 RNA ≥50 c/mL and must be performed at the Week 28, Week 52, Week 100 and Week 148 study visits respectively, so long as the guidelines provided above for scheduling confirmatory HIV-1 RNA assessment to avoid false-positive results have been followed.

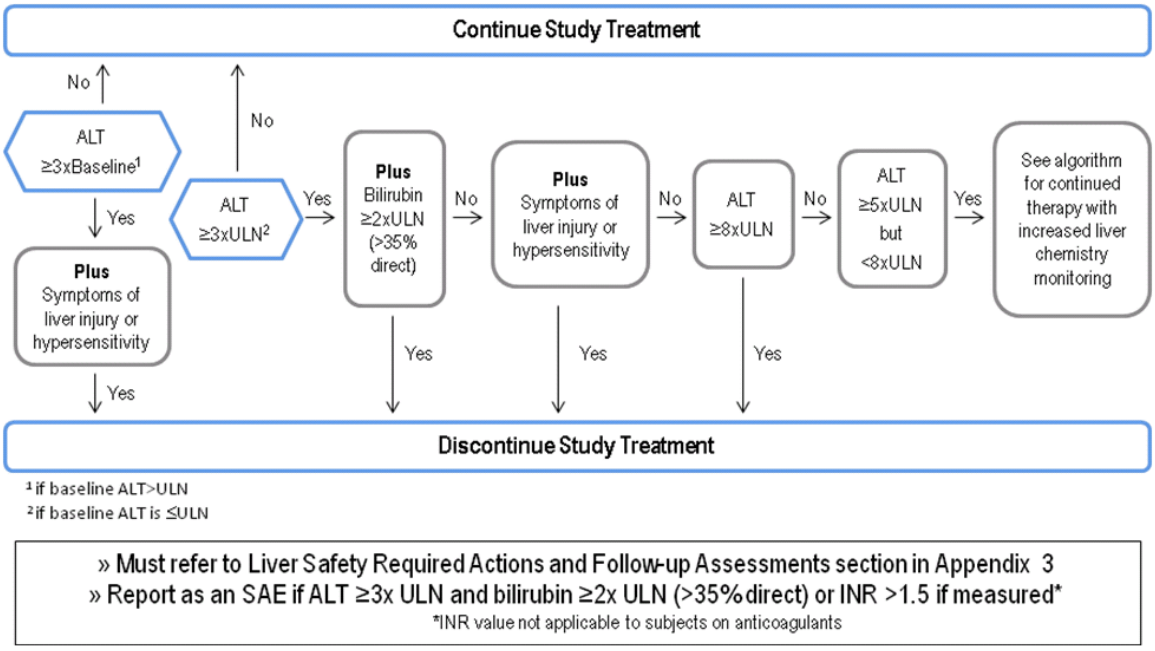
NOTE: Subjects whose HIV-1 RNA is <50 c/mL at Weeks 24, 48 and 96 will not attend the Week 28, Week 52 and Week 100 study visits, respectively.

5.4.2. Liver Chemistry Stopping Criteria

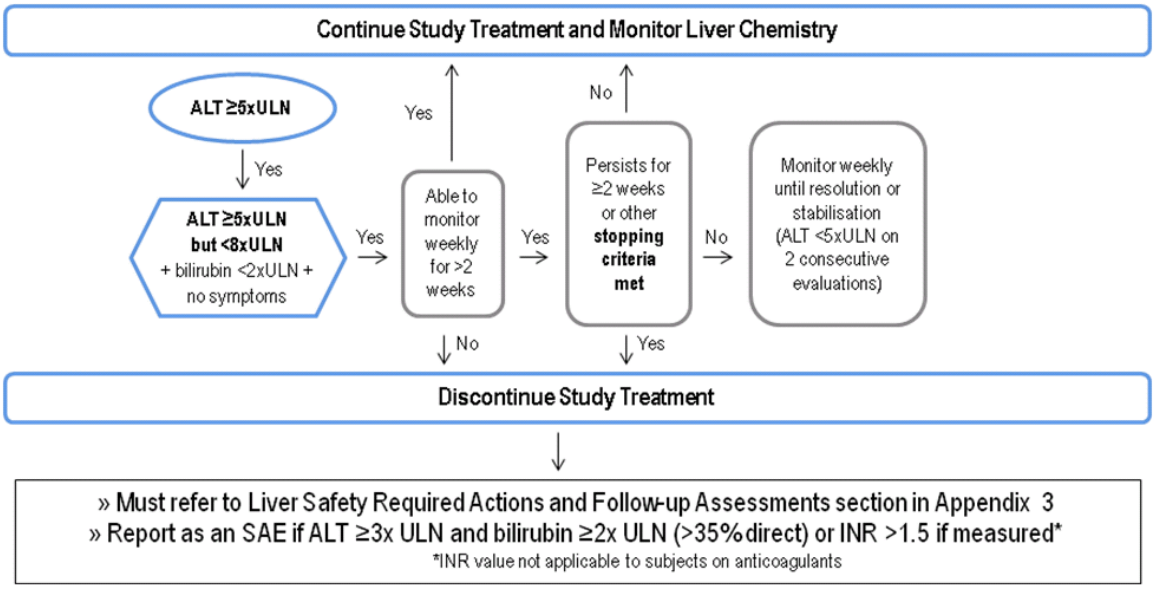
Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event aetiology (in alignment with the FDA premarketing clinical liver safety guidance).

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

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 Appendix 3, Section 12.3.

5.4.2.1. Study Treatment Restart

If a subject meets liver chemistry stopping criteria do not restart the subject 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 is signed by the subject.

Refer to Appendix 4, Section 12.4 for full guidance.

5.5. Subject and Study Completion

Subjects are considered to have completed the study if they satisfy one of the following:

- Randomly assigned to either treatment arm, completed the Open-label Randomised Phase including the Week 148 visit, and did not enter the Continuation Phase;
- Randomly assigned to DTG plus 3TC, completed the Open-label Randomised Phase including the Week 148 visit, entered and completed the Continuation Phase (defined as remaining on study 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 available or development of the DTG plus 3TC dual regimen is terminated).

Subjects with ongoing AEs or laboratory abnormalities considered to be AEs will attend a Follow-up visit approximately four weeks after their last dose of study treatment. The Follow-up visit is not required for successful completion of the study.

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

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

The term 'study treatment' is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

	Study Treatment (Double-blind Randomised Phase, Day 1 to Week 96)		
Product name:	Dolutegravir, DTG	Lamivudine, 3TC	Tenofovir disoproxil fumarate/emtricitabine fixed-dose combination, TDF/FTC FDC
Formulation description:	Clinical trial material, which is the same formulation as the commercial material with the exception of the film coat colour	Over-encapsulated commercial supply tablet to visually match over-encapsulated TDF/FTC FDC tablet	Over-encapsulated commercial supply tablet to visually match over-encapsulated 3TC tablet
Dosage form:	Tablet	Capsule	Capsule
Unit dose strength(s)/Dosage level(s):	50 mg	300 mg	300 mg TDF/200 mg FTC
Route of Administration:	Oral	Oral	Oral
Dosing instructions:	Take one tablet once daily with or without food	Take one capsule once daily with or without food	Take one capsule once daily with or without food
Physical description:	White, round, biconvex, film-coated tablets debossed on one side with “SV 572” and on the other side with “50”. The tablets are packaged into high density polyethylene (HDPE) bottles with induction seals and child-resistant closures. Each 45 ml bottle contains 30 tablets and a desiccant.	Swedish Orange, size AA elongated double-blind hydroxypropyl methylcellulose (HPMC) capsules. The capsules are packaged into HDPE bottles with induction seals and child- resistant closures. Each 150 mL bottle contains 30 capsules and a desiccant.	Swedish Orange, size AA elongated double-blind HPMC capsules. The capsules are packaged into HDPE bottles with induction seals and child-resistant closures. Each 150 mL bottle contains 30 capsules and a desiccant.

	Study Treatment (Open-label Randomised Phase, Week 96 to Week 148)		
Product name:	Dolutegravir, DTG	Lamivudine, 3TC	Tenofovir disoproxil fumarate/emtricitabine fixed-dose combination, TDF/FTC FDC
Formulation description:	Clinical trial material, which is the same formulation as the commercial material with the exception of the film coat colour	Commercial supply	Commercial supply
Dosage form:	Tablet	Tablet	Tablet
Unit dose strength(s)/Dosage level(s):	50 mg	300 mg	300 mg TDF/200 mg FTC
Route of Administration:	Oral	Oral	Oral
Dosing instructions:	Take one tablet once daily with or without food	Take one tablet once daily with or without food	Take one tablet once daily with or without food
Physical description:	White, round, biconvex, film-coated tablets debossed on one side with “SV 572” and on the other side with “50”. The tablets are packaged into HDPE bottles with induction seals and child-resistant closures. Each 45 ml bottle contains 30 tablets and a desiccant.	White, diamond-shaped, scored, film-coated tablets debossed with “GX CJ7” on both sides. The tablets are packed in over-labelled HDPE bottles with child-resistant closures each containing 30 tablets.	Blue, capsule-shaped, film-coated tablet, debossed on one side with “GILEAD” and on the other side with “701”. The tablets are packed in over-labelled HDPE bottles with polypropylene child-resistant closures each containing 30 tablets and a desiccant.

	Study Treatment (Continuation Phase)	
Product name:	Dolutegravir, DTG	Lamivudine, 3TC
Formulation description:	Clinical trial material, which is the same formulation as the commercial material with the exception of the film coat colour	Commercial supply
Dosage form:	Tablet	Tablet
Unit dose strength(s)/Dosage level(s):	50 mg	300 mg
Route of Administration:	Oral	Oral
Dosing instructions:	Take one tablet once daily with or without food	Take one tablet once daily with or without food
Physical description:	White, round, biconvex, film-coated tablets debossed on one side with "SV 572" and on the other side with "50". The tablets are packaged into HDPE bottles with induction seals and child-resistant closures. Each 45 ml bottle contains 30 tablets and a desiccant.	White, diamond-shaped, scored, film-coated tablets debossed with "GX CJ7" on both sides. The tablets are packed in over-labelled HDPE bottles with child-resistant closures each containing 30 tablets.

6.2. Treatment Assignment

Informed consent must be obtained prior to any study procedures, including any screening assessment. Subjects will be assigned to study treatment in accordance with the computer-generated randomisation schedule. The central randomisation schedule will be generated by PPD using a validated SAS developed program.

Randomisation and study treatment assignment 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 register subjects. Subjects will be randomized in a 1:1 ratio to DTG plus 3TC or DTG plus TDF/FTC FDC in accordance with the computer-generated randomisation schedule. Each subject will be assigned a unique identifier (designating the subject's randomisation code) and a unique treatment number, which matches the randomised treatment assignment.

Subjects will maintain the assigned treatment group throughout both the Double-blind Randomised Phase (Day 1 to Week 96) and the Open-label Randomised Phase (Week 96 to Week 148).

Subjects who are randomly assigned into the study and subsequently withdrawn may not be rescreened. Once a randomisation number has been assigned it must not be re-assigned.

6.3. Blinding

Participants and investigators will remain blinded during the Double-blind Randomised Phase. The sponsor will be unblinded at Week 24 in order to provide results from the 24-week interim analysis to regulatory authorities but no external dissemination of results will occur until at least all the patients are through the primary time point, i.e. Week 48.

Subjects will receive open-label DTG plus double-blinded 3TC or open-label DTG plus double-blinded TDF/FTC FDC therapy during the Double-blind Randomised Phase (i.e. through their Week 96 study visit). Study treatment during the Open-label Randomised Phase after Week 96 up to Week 148 will be unblinded.

6.3.1. Emergency Unblinding

- The investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the investigator.
- Investigators have direct access to the subject's individual study treatment.
- It is preferred (but not required) that the investigator first contacts the Medical Monitor or appropriate ViiV Healthcare/GSK/PPD study personnel to discuss options **before** unblinding the subject's treatment assignment.
- If ViiV Healthcare/GSK/PPD personnel are not contacted before the unblinding, the investigator must notify ViiV Healthcare/GSK/PPD as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study.
- The date and reason for the unblinding must be fully documented in the case report form (CRF).

A subject will be withdrawn if the subject's treatment code is unblinded by the investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the CRF.

- GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to investigators in accordance with local regulations and/or ViiV Healthcare/GSK policy.

6.3.2. Scheduled Unblinding

Investigators will unblind all subjects to study treatment as they complete the Week 96 visit (see Section 7.1) prior to subjects entering the Open-label Randomised Phase (Week 96 to Week 148).

6.4. Packaging and Labeling

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

6.5. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required.

- 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 subjects enrolled in the study may receive study treatment and only authorised site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the Study Reference Manual (SRM).
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
- A 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.

6.6. Compliance with Study Treatment Administration

Study treatment accountability will be evaluated using pill counts of unused study treatments (DTG plus 3TC or DTG plus TDF/FTC FDC). This assessment will be conducted each time the subject receives a new (refill) supply of study treatments through the Withdrawal visit or study completion. These data will be recorded in the subject's CRF but will not be summarised for analysis purposes.

6.7. Treatment of Study Treatment Overdose

For this double-blind study, any tablet intake exceeding the randomised daily number of tablets for study treatment will be considered an overdose (see [TIVICAY Product Information, 2015]; [EPIVIR Product Information, 2015]; [Truvada Product Information, 2016]). 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 12.7.1) 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 12.7.2).

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.

6.8. Treatment after the End of the Study

Prior to completion of the Week 148 visit, randomised subjects will need to have alternative arrangements in place for access to antiretroviral medication. If required by local regulations, subjects randomised to receive DTG plus 3TC once daily therapy and who have successfully completed both the 96 weeks of treatment in the Double-blind Randomised Phase and the Open-label Randomised Phase through Week 148 will be given the opportunity to continue to receive DTG plus 3TC once daily (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 available, or
- the subject no longer derives clinical benefit, or
- the subject meets a protocol-defined reason for discontinuation, or
- development of the DTG plus 3TC dual regimen is terminated.

Subjects randomised to the DTG plus TDF/FTC FDC arm will receive DTG plus TDF/FTC FDC through their Week 148 visit only, after which subjects will complete the study and will need to have alternate arrangements in place to access antiretroviral medication.

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

6.9. Concomitant Medications and Non-Drug Therapies

Subjects 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, especially if any new concomitant medications are reported by subjects. All concomitant medications taken during the study will be recorded in the eCRF. The minimum requirement is that the drug name, route, and the dates of administration are to be recorded.

6.9.1. 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 6.9.2). Chemoprophylaxis for HIV-associated conditions is encouraged, if appropriate, at the discretion of the subject 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 minimise the risk of non-specific increases in the level of HIV-1 plasma RNA at the next scheduled assessment.

DTG plus 3TC and DTG plus TDF/FTC FDC should be administered 2 hours before OR 6 hours after taking polyvalent cation-containing antacids. Proton pump inhibitors and H2-antagonists may be used in place of antacids with no scheduling restrictions. Concurrent administration with multivitamins is acceptable. Calcium or iron supplements can be taken with study treatment provided that all are taken together with a meal. Under fasted conditions, DTG 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 with metformin, to maintain glycaemic control.

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

6.9.2. Prohibited Medications and Non-Drug Therapies

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

- HIV immunotherapeutic vaccines (see Section 6.9.1 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 5.2).
- Systemically administered immunomodulators (such as interleukin and interferon agents) are prohibited through Week 148 (a list of examples is provided in the SRM). 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 of the Double-blind Randomised Phase; 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.
- 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.

- Carbamazepine
- Oxcarbamazepine
- Phenobarbital
- Phenytoin
- Rifampicin or rifapentine
- St. John's wort (*Hypericum perforatum*)

Dofetilide and pilsicainide are prohibited as DTG may inhibit their renal tubular secretion resulting in increased dofetilide/pilsicainide 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. STUDY ASSESSMENTS AND PROCEDURES

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

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table, Section 7.1.

7.1. Time and Events Table

Procedures	Screening Visit[a]	Double-blind Randomised Phase													Open-label Randomised Phase						Continuation Phase[c]	Withdrawal	Follow-up[d]
		Baseline / Day 1	Week 4	8	12	16	24	28[b]	36	48	52[b]	60	72	84	96	100[b]	108	120	132	144	148	Every 12 weeks after Week 148		
Clinical and Other Assessments																								
Written informed consent	X																							
Inclusion/Exclusion criteria[e]	X	X																						
Demography	X																							
Prior ART history	X																							
Medical history[f]	X																							
Current medical conditions	X																							
Cardiovascular risk assessment, including vital signs[g]	X																							
HIV risk factors and mode of transmission		X																						
CDC HIV-1 classification	X	X																						
HIV associated conditions			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Columbia Suicidality Severity Rating Scale		X[h]	X	X	X	X	X		X	X		X	X	X	X		X	X	X	X		X	X	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Symptom Directed Physical Exam/Medical Decision Making[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
12-lead ECG[j]	X																							

Procedures	**Screening Visit**[a]	**Double-blind Randomised Phase**														**Open-label Randomised Phase**						**Continuation Phase**[c]	**Withdrawal**	**Follow-up**[d]
		Baseline / Day 1	**Week**																					
			4	**8**	**12**	**16**	**24**	**28**[b]	**36**	**48**	**52**[b]	**60**	**72**	**84**	**96**	**100**[b]	**108**	**120**	**132**	**144**	**148**	**Every 12 weeks after Week 148**		
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious adverse events	X[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EQ-5D-5L[l]		X	X				X			X					X					X			X	
Laboratory Assessments																									
Plasma for HIV genotyping	X																								
Quantitative plasma HIV-1 RNA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[m]	X	X	X	
Lymphocyte subset	X	X	X	X	X	X	X		X	X		X	X	X	X		X	X	X	X	X		X	X	
Plasma for storage[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical chemistry	X	X	X	X	X	X	X		X	X		X	X	X	X		X	X	X	X	X		X	X	X
Haematology	X	X	X	X	X	X	X		X	X		X	X	X	X		X	X	X	X	X		X	X	X
PT/INR	X																								
Fasting lipids and glucose[o]		X					X			X					X					X			X[p]	
Urinalysis and spot urine for protein analysis[q]		X					X			X					X					X			X	X
Pregnancy test[r]	S	U	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	
HBsAg, anti-HBc, anti-HBs, and HBV DNA[s]	X																								
HCV antibody	X																								
RPR	X																								
Renal and bone marker analytes (blood/urine)[t]		X					X			X					X					X			X	
PBMCs[u]		X																			X[u]		X[u]	

Procedures	Screening Visit[a]	Double-blind Randomised Phase														Open-label Randomised Phase						Continuation Phase[c]	Withdrawal	Follow-up[d]
		Baseline / Day 1	Week																					
			4	8	12	16	24	28[b]	36	48	52[b]	60	72	84	96	100[b]	108	120	132	144	148	Every 12 weeks after Week 148		
Study Treatment																								
IVRS/IWRS[v]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense study treatment		X	X	X	X	X	X		X	X		X	X	X	X		X	X	X	X	X	X		
Study treatment accountability (pill counts)			X	X	X	X	X		X	X		X	X	X	X		X	X	X	X	X	X	X	

anti-HBc = antibody to hepatitis B core antigen, anti-HBs = hepatitis B surface antibody, ART = antiretroviral therapy, CDC = Centers for Disease Control and Prevention, DNA = deoxyribonucleic acid, ECG = electrocardiograph, HBsAg = hepatitis B surface antigen, HCV = hepatitis C virus, HIV-1 = human immunodeficiency virus type 1, INR = international normalised ratio, IVRS = interactive voice recognition system, IWRS = interactive web recognition system, PBMC = peripheral blood mononuclear cell, PT = prothrombin time, RNA = ribonucleic acid, RPR = rapid plasma reagin

a. Randomisation may occur as soon as all Screening results are available.

b. Subjects with plasma HIV-1 RNA levels ≥50 c/mL at Week 24, Week 48 and Week 96 must have HIV-1 levels re-assessed by a second measurement performed four weeks later at the Week 28, Week 52 visit and Week 100 visit, respectively. Subjects should have received full doses of study treatment for at least 2 weeks at the time of HIV-1 RNA re-assessment for any HIV-1 RNA level ≥50 c/mL. Subjects with plasma HIV-1 RNA levels <50 c/mL at Week 24, Week 48 and Week 96 should not attend the Week 28 visit, Week 52 visit and Week 100 visit, respectively.

c. Subjects randomised to DTG plus 3TC who complete through Week 148 may enter the Continuation Phase. Subjects completing the Continuation Phase must return to the clinic for an End of Continuation Phase visit when transitioning to commercial supplies or to an alternate ART regimen if appropriate. At this visit, conduct study assessments as specified for all Continuation Phase visits with the exception of dispensing study treatment.

d. An in-clinic Follow-up visit will be conducted 4 weeks after the last dose of study medication for subjects with the following conditions at the last on-study visit: ongoing AEs, serious adverse events (SAEs) regardless of attributability, any laboratory abnormalities considered to be AEs or potentially harmful to the subject.

e. 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.

f. Full medical history will be conducted prior to randomisation 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.

g. Assessment for cardiovascular risk will include height, weight, blood pressure, smoking status and history, pertinent medical conditions (e.g., hypertension, diabetes mellitus), and family history of premature cardiovascular disease. Body mass index (BMI) will be calculated within the eCRF.

h. On Day 1, the electronic Columbia Suicidality Severity Rating Scale (eC-SSRS) is to be administered prior to randomisation.

i. Limited physical examination to include blood pressure at Day 1 (recorded in eCRF) for Framingham score assessment. Blood pressure to be measured after resting in a semi-supine position for at least 5 minutes.
j. A 12-lead ECG will be performed after resting in a semi-supine position for at least 5 minutes.
k. Only SAEs related to study participation or to a concomitantly administered ViiV Healthcare/GSK product will be collected between obtaining informed consent and administration of study drug at Day 1.
l. The questionnaire is recommended to be administered at the beginning of the visit before any other assessments are conducted. Only conduct the questionnaire at Withdrawal if occurring prior to Week 144.
m. At Week 148, repeat HIV-1 RNA testing will only be performed for subjects with HIV-1 RNA ≥50 c/mL at Week 144.
n. Plasma samples for storage will be collected at each visit, including unscheduled visits (e.g. for HIV-1 RNA levels and immunological parameters). Additionally, these samples will be used when needed such as when samples are lost or arrive at the laboratory unevaluable or as a priority need for genotypic and/or phenotypic analyses when subjects meet CVW criteria.
o. An overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable.
p. Only collect fasting lipids and glucose if the Withdrawal visit occurs at Week 24, Week 48, Week 96 or Week 144.
q. A morning specimen is preferred. To assess renal biomarkers: urine albumin/creatinine ratio; urine protein/creatinine ratio; and urine phosphate.
r. 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.
s. HBV DNA testing will be performed for subjects with positive anti-HBc and negative HBsAg and negative anti-HBs (past and/or current evidence). Subjects will have to return to the clinic to provide a sample for HBV DNA testing prior to randomisation.
t. Blood samples for renal and bone biomarker assessments: **Renal:** Cystatin C; Beta-2 Microglobulin; Retinol Binding Protein (RBP); **Bone:** bone specific alkaline phosphatase, procollagen type I N-terminal propeptide, type I collagen cross-linked C-telopeptide, osteocalcin, 25-hydroxyvitamin D. Urine sample for renal biomarker assessments: RBP and Beta-2-Microglobulin. Only collect at the Withdrawal visit if it occurs at Week 24, Week 48, Week 96 or Week 144.
u. Whole blood/PBMC collection samples may be used for virologic analyses as described in the protocol. A sample at Day 1 and a second sample at either Week 148 or at Withdrawal (if a subject is withdrawn prior to Week 148) will be taken for all subjects.
v. At Screening, a subject number will be generated.

7.2. Screening and Critical Baseline Assessments

Written informed consent must be obtained from each potentially eligible subject (or his/her legal representative) by study site personnel prior to the initiation of any Screening procedures as outlined in this protocol. The consent form must have been approved by the IRB/Independent Ethics Committee (IEC). After signing an informed consent, subjects will complete Screening assessments to determine subject eligibility. Each subject being screened for study enrolment evaluation will be assigned a subject number at the Screening visit. This number will be given sequentially in chronological order of subject presentation according to a numeric roster provided by GSK/PPD.

7.2.1. Screening Assessments

Assessments to be conducted at Screening are provided in the Time and Events Table (Section 7.1).

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.

Cardiovascular medical history/risk factors (as detailed in the CRF) will be assessed at screening and assessments will include height, weight, blood pressure, smoking status and history, pertinent medical conditions (e.g. hypertension, diabetes mellitus), and family history of premature cardiovascular disease.

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.

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 subjects must provide a plasma sample for determination of viral genotypic resistance at 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 [IAS-USA, 2014]. The study virologists will confirm the lack or presence of exclusionary resistance mutations, and communicate eligibility based on the resistance test results.

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 subjects with a CrCL <50 mL/min per 1.73 m^2 are excluded due to requirements for dose reduction of 3TC or dose interval adjustments of TDF/FTC in patients with renal dysfunction.

Subjects 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 randomisation for subjects with positive anti-HBc and both negative HBsAg and anti-HBs (past and/or current evidence).

All subjects will be screened for syphilis using a rapid plasma reagin (RPR) at Screening. Subjects with untreated syphilis infection, defined as a positive RPR without clear documentation of treatment, are excluded. Subjects with a positive RPR test who have not been treated may be rescreened at least 14 days after completion of antibiotic treatment for syphilis.

Subjects who meet all entry criteria may be randomly assigned as soon as all Screening assessments are complete and the results are available and documented. All subjects will complete the Screening period of approximately 28 days (extendable to 35 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 randomisation.

Subjects not meeting all inclusion and exclusion criteria at initial screen may be rescreened and receive a new subject number one time unless they were excluded for reason of having exclusionary historic genotypic resistance. Subjects who are randomised into the trial and subsequently withdrawn from the study for any reason may not be rescreened.

7.2.2. Baseline Assessments

Assessments to be conducted at Baseline (Day1) are provided in the Time and Events Table (Section 7.1).

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

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

7.3. Efficacy

Plasma HIV-1 RNA

Plasma for quantitative HIV-1 RNA will be collected according to the Time and Events Table (Section 7.1). 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 characterise 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 Time and Events Table (Section 7.1).

CDC HIV-1 Classification and HIV Associated Conditions

HIV-associated conditions will be recorded as per the Time and Events Table (Section 7.1). HIV associated conditions will be assessed according to the 2014 CDC Classification System for HIV Infection in Adults (see Appendix 5, Section 12.5). Indicators of clinical disease progression are defined as:

CDC Stage 1 at enrolment → Stage 3 event;

CDC Stage 2 at enrolment → Stage 3 event;

CDC Stage 3 at enrolment → New Stage 3 Event;

CDC Stage 1, 2 or 3 at enrolment → Death.

7.4. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1).

7.4.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

The definitions of an AE or SAE can be found in Appendix 7, Section 12.7.

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

7.4.1.1. Time period and Frequency for collecting AE and SAE information

- Any SAEs assessed as related to study participation (e.g. protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a ViiV Healthcare/GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- AEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.4.1.3), at the time points specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- All SAEs will be recorded and reported to the Medical Monitor within 24 hours, as indicated in Appendix 7, Section 12.7.7.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any

time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify the Medical Monitor.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to ViiV Healthcare/GSK/PPD are provided in Appendix 7, Section 12.7.

7.4.1.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

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

7.4.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, until the condition stabilises, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 7, Section 12.7.

7.4.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 7 (Section 12.7.3) and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs 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 CRF 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.

7.4.1.5. 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 5, Section 12.5) 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/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 12.7.2), or
- The event or outcome is in the investigator's opinion of greater intensity, frequency or duration than expected for the individual subject, 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.

7.4.1.6. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to ViiV Healthcare or designee of SAEs related to study treatment is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product 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 product under clinical investigation. ViiV Healthcare/GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/ IEC and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and ViiV Healthcare/GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE(s) or other specific safety information (e.g. summary or listing of SAEs) from ViiV Healthcare/GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

7.4.2. Pregnancy

- Details of all pregnancies in female subjects will be collected after the start of dosing and until and ending at the final Follow-up visit.
- If a pregnancy is reported then the investigator should inform ViiV Healthcare/GSK/PPD within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 9, Section 12.9.2.

7.4.3. Physical Exams

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

7.4.4. Electrocardiogram (ECG)

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).

7.4.5. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Section 7.1, must be performed by the central laboratory, Q^2 Solutions, or a laboratory contracted by the central laboratory. Laboratory assessments must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by Q^2 Solutions and are detailed in the laboratory manual. Reference ranges for all safety parameters will be provided to the site by Q^2 Solutions.

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

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

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

Table 1 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Haematology	Platelet Count; RBC Count; WBC Count (absolute); Haemoglobin; Haematocrit *RBC Indices*: MCV; MCH *Automated WBC Differential:* Neutrophils; Lymphocytes; Monocytes; Eosinophils; Basophils
Clinical Chemistry [1]	BUN; Chloride; Alkaline phosphatise; Creatine phosphokinase Creatinine; Calcium; Phosphate; Creatinine clearance [4] Glucose [2]; Total CO_2; Total bilirubin [3]; Lipase Potassium; AST; Total protein Sodium; ALT; Albumin
Fasting Lipid Panel [5]	• Total cholesterol • HDL cholesterol • LDL cholesterol • Triglycerides
Other Laboratory Tests	• Plasma HIV-1 RNA [6] • CD4+ cell counts • Hepatitis B (HBsAg, anti-HBc, anti-HBs, HBV DNA) • Hepatitis C (anti-HCV) • RPR • PT/INR • Serum hCG pregnancy test (as needed for females of reproductive potential) [7] • Urinalysis, urine albumin/creatinine ratio, and urine protein/creatinine ratio, urine phosphate • Renal biomarkers including Cystatin C (blood), Retinol Binding Protein (RBP, blood/urine); and Beta-2 Microglobulin (B2M, blood/urine) [8] • Bone biomarkers including: bone-specific alkaline phosphatase, procollagen type I N-terminal propeptide, type I collagen cross-linked C-telopeptide, osteocalcin, 25-hydroxyvitamin D [8]

ALT = alanine aminotransferase, anti-HBc = hepatitis B core antibody, anti-HBs = hepatitis B surface antibody, anti-HCV = hepatitis C antibody, AST = aspartate aminotransferase, BUN = blood urea nitrogen, CO_2 = carbon dioxide, HBsAg = hepatitis B surface antigen, HBV DNA = hepatitis B virus deoxyribonucleic acid, HDL = high density lipoprotein, LDL = low density lipoprotein, MCH = mean corpuscular haemoglobin, MCV = mean corpuscular volume, PT/INR = prothrombin time/international normalised ratio, RBC = red blood cells, RPR = rapid plasma reagin, WBC = white blood cells

NOTES :

1. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-up Assessments after liver stopping or monitoring event are given in Section 5.4.2 and Appendix 3, Section 12.3. Details of

other stopping/withdrawal criteria and Toxicity Management are given in Section 5.4 and Appendix 8, Section 12.8.

2. For fasting glucose assessments, an overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable for subjects with afternoon appointments.
3. Direct bilirubin will be reflexively performed for all total bilirubin values >1.5× ULN.
4. Glomerular filtration rate (GFR) will be estimated by the central laboratory using the CKD-EPI method [Levey, 2009].
5. For fasting lipids assessments, an overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable for subjects with afternoon appointments.
6. For subjects meeting virologic withdrawal criteria, plasma samples will be analysed in attempt to obtain genotype/phenotype data.
7. Pregnancy testing will be conducted on serum samples with the exception of Day 1, when a urine test is used to confirm status prior to administration of study treatment.
8. Since the intention is to utilise these biomarker data for research purposes, the sponsor will not be reporting the results of these assessments to the investigator, except for some individual renal biomarkers and 25-hydroxyvitamin D. No summary analysis of biomarker data will be made until a study endpoint is reached.

All laboratory tests with values that are 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. If such values do not return to normal within a period judged reasonable by the investigator, the aetiology should be identified and the sponsor notified.

7.4.6. Suicidal Risk Monitoring

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

Subjects should be monitored appropriately and observed closely for suicidal ideation and behaviour or any other unusual changes in behaviour. It is recommended that the investigator consider mental health consultation or referral for subjects who experience signs of suicidal ideation or behaviour. Subjects 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.

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 behavioural suicidal events used in this scale are based on those used in the Columbia Suicide History Form [Posner, 2007]. Questions are asked on suicidal behaviour, 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) and all subsequent questioning in relation to the last assessment. The eC-SSRS is to be administered as a patient completed questionnaire specified in the Time and Events Table (Section 7.1). 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 subject 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 behaviour, 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/PPD within 1 week of the investigator diagnosing a possible suicidality-related AE.

7.5. Biomarkers

Blood and urine are being collected to perform renal and bone biomarker assessments as outlined in Section 7.1.

Renal biomarkers include:

- Cystatin C (blood)
- Retinol Binding Protein (RBP, blood/urine),
- Beta-2-Microglobulin (B2M, blood/urine),
- urine albumin/creatinine ratio,
- urine protein/creatinine ratio,
- urine phosphate, and
- serum creatinine.

Bone biomarkers (blood) include:

- bone-specific alkaline phosphatase,
- procollagen type 1 N-propeptide,
- type 1 collagen cross-linked C-telopeptide,
- osteocalcin, and
- 25-hydroxyvitamin D.

Since the intention is to utilise these biomarkers for research purposes, the Sponsor will not be reporting the results of these assessments to the investigator except for some renal biomarkers and 25-hydroxyvitamin D. No summary analysis of biomarker data will be made until a study endpoint is reached.

7.6. HIV-1 Polymerase Viral Genotyping and Phenotyping

Whole venous blood samples will be obtained from each subject to provide plasma for storage samples according to the Time and Events Table (Section 7.1). Subjects meeting CVW criteria will have plasma samples tested for HIV-1 PRO and RT genotype and phenotype and HIV-1 integrase genotype and phenotype from Baseline samples and from samples collected at the time of meeting SVW criteria; these results will be reported to the investigator as soon as available to provide guidance for election of an alternative regimen. See Section 5.4.1.3 for details.

Details concerning the handling, labelling and shipping of these samples will be supplied separately. Genotypic analyses for RT and PRO will be carried out at Screen by Q^2 Solutions, and genotypic and phenotypic analyses may be carried out by Monogram Biosciences using, but not limited to, their Standard PhenoSense and GenoSure testing methods for PRO, RT, and integrase.

7.6.1. HIV-1 Exploratory Analyses

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

Additional virologic analyses for HIV-1 may, for example, be carried out on peripheral blood mononuclear cell (PBMC) samples collected at Baseline or on study per Time and Events Table (Section 7.1), 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 PRO and RT genotype and phenotype and HIV-1 integrase genotype and phenotype will also be determined on the last on-treatment isolates from subjects who at that time point (e.g. Withdrawal visit) have HIV-1 RNA ≥400 c/mL while receiving study treatment regardless of confirmatory HIV-1 RNA.

7.7. Value Evidence and Outcomes

The Health outcomes assessment will be conducted according to the Time and Events Table (Section 7.1). The assessment is recommended to be administered at the beginning of the visit prior to collection of blood for analysis and other scheduled assessments. The questionnaire will be administered on paper.

The European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L), developed by EuroQol group, is a standardised, generic questionnaire that provides a profile of patient function and a global health state rating. The five-item measure has one question assessing each of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression and 5 levels for each dimension including no problems, slight problems, moderate problems, severe problems and extreme problems. The EQ-5D-5L also includes a visual analogue scale (VAS) that assesses overall health [Herdman, 2011].

7.7.1. Value Evidence and Outcomes Endpoints

- Summary statistics as well as between and within group change from Baseline in health related quality of life using EQ-5D-5L at Weeks 4, 24, 48, 96, and 144 (or Withdrawal from the study).

8. DATA MANAGEMENT

- For this study, subject data will be entered into GSK-defined CRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable PPD standards and data cleaning procedures to ensure the integrity of the data, e.g. removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA and an internal validated medication dictionary, GSKDrug.
- eCRFs (including queries and audit trails) will be retained by GSK, and copies will be sent at the end of the study in CD format to GSK to be retained. Each investigator will receive a copy of his or her site-specific data in the same format to maintain as the investigator copy. Subject initials will not be collected or transmitted to ViiV Healthcare/GSK according to ViiV Healthcare/GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

This study is designed to show that the antiviral effect of a simplified two-drug regimen of DTG plus 3TC once-daily is not inferior to a standard three-drug regimen of DTG plus TDF/FTC FDC once daily in HIV-1 infected ART-naïve adult subjects.

Non-inferiority can be concluded if the lower bound of a two-sided 95% confidence interval for the difference in response rates between the two treatment arms is greater than -10%. If r_d is the response rate on DTG plus 3TC and r_f is the response rate on DTG plus TDF/FTC FDC, then the hypotheses can be written as follows:

$$H_0: r_d - r_f \leq -10\% \qquad H_1: r_d - r_f > -10\%$$

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

Assuming a true response rate of 87% for the DTG plus 3TC arm and an 89% response rate for the DTG plus TDF/FTC arm, the study requires 347 subjects per arm to have 90% power with a 10% non-inferiority margin and a 2.5% one-sided alpha level.

9.2.1.1. Rationale for non-inferiority margin

The use of a 10% non-inferiority margin for treatment-naïve subjects is in accordance with current FDA guidance [CDER, 2015].

9.2.1.2. Response rate assumptions

Response rates at week 48 in previous studies with DTG plus two NRTIs range from 85% - 90% (Table 2). The response rate on the DTG plus TDF/FTC arm is assumed to be 89% at Week 48 based on the combined evidence. Response rates at Week 48 in previous two-drug regimen studies range from 83% - 88% (Table 2). However, there is no previous two-drug regimen study conducted with DTG. The response rate on the DTG plus 3TC arm at week 48 is assumed to be 87% combining evidence from both previous DTG studies and studies with other two-drug regimen.

Table 2 Response rates in previous DTG and two-drug regimen studies

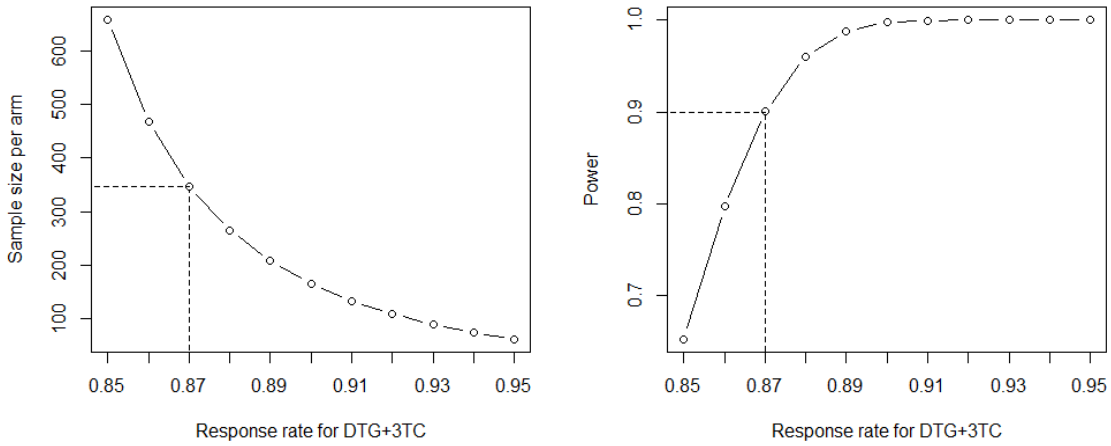
	n	Treatment regimen	Week 48 response rate (<50 c/mL)
SPRING-2[1]	411	DTG + 2 NRTIs (ABC/3TC or TDF/FTC)	88%
SINGLE[2]	414	DTG + ABC/3TC	88%
FLAMINGO[3]	242	DTG + 2 NRTIs (ABC/3TC or TDF/FTC)	90%
ACTG A5142[4]	250	LPV/RTV + EFV	83%
PROGRESS[5]	101	LPV/RTV+ RAL	83%
GARDEL[6]	214	LPV/RTV + 3TC	88%

[1] [Raffi, 2013]
[2] [Walmsley, 2013]
[3] [Clotet, 2014]
[4] [Riddler, 2008]; Week 96 response rates are shown.
[5] [Reynes 2011]
[6] [Cahn, 2014]

9.2.2. Sample Size Sensitivity

Figure 2 shows sensitivity of the required sample size to the true response rate for the DTG plus 3TC arm assuming an 89% response rate in the DTG plus TDF/FTC arm.

Figure 2 Sample Size Sensitivity



9.2.3. Sample Size Re-estimation or Adjustment

No sample size re-estimation will be performed.

9.3. Data Analysis Considerations

The following populations will be assessed. The analysis population for genotypic and phenotypic analyses will be fully described in the reporting and analysis plan (RAP).

9.3.1. Analysis Populations

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

This population will consist of all randomised subjects who receive at least one dose of study medication. Subjects will be assessed according to their randomised treatment, regardless of the treatment they receive. Unless stated otherwise, the ITT-E Population will be used for efficacy analyses.

9.3.1.2. Per Protocol (PP) Population

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

9.3.1.3. Safety Population

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

9.3.2. Analysis Data Sets

Subjects' responses at <50 c/mL will be calculated according to a Missing, Switch or Discontinuation = Failure (MSD=F) algorithm – as codified by the FDA's snapshot algorithm. This algorithm treats all subjects 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 subjects who switch their concomitant ART prior to the visit of interest since no switches are allowed in this protocol.

Otherwise, virologic success or failure will be determined by the last available HIV-1 RNA assessment while the subject is on-treatment within the visit of interest window (as specified in the RAP).

Full details of this snapshot algorithm will be contained in the RAP.

A secondary set of data will treat subjects 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 will be the primary dataset for assessing safety.

9.3.3. Treatment Comparisons

9.3.3.1. Primary Comparison of Interest

The primary analysis will be based on the ITT-E population using the Snapshot dataset. The primary comparison will be made at a one-sided 2.5% level of significance. Treatment with DTG plus 3TC will be declared non-inferior to treatment with DTG plus TDF/FTC FDC if the lower end of a two-sided 95% confidence interval for the difference between the two groups in response rates at Week 48 lies above -10%.

9.3.3.2. Other Comparisons of Interest

The analysis described above will also be performed using the PP population and the results will be compared for consistency with the results from the ITT-E population. If both analyses show non-inferiority then the hypothesis that the antiviral effect of treatment with DTG plus 3TC is superior to treatment with DTG plus TDF/FTC FDC will be tested using the same level of significance as for the tests of non-inferiority. Superiority will be declared if the lower end of the confidence internal is above 0%. The primary comparison will also be performed using the ITT population and will be compared for consistency with the results from the ITT-E and PP populations.

9.3.3.3. Secondary comparisons

The following key secondary comparison will be tested:

- Superiority of DTG plus 3TC compared to DTG plus TDF/FTC FDC with respect to change from baseline in CD4+ cell counts;

- Superiority of DTG plus 3TC compared to DTG plus TDF/FTC FDC with respect to renal biomarkers, RBP and B2M.

No multiplicity adjustments for statistical testing of secondary endpoints will be performed; however, all tests will be pre-specified in the RAP.

9.3.4. Interim Analyses

At least four analyses will be conducted to evaluate primary and secondary objectives of the protocol, one when all subjects have completed their visits at Week 24, at Week 48, at Week 96, and at Week 144. Further data cuts and analyses may be conducted as necessary after Week 144 in order 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 24, Week 96 and Week 144 analyses will be secondary. ViiV Healthcare/GSK/PPD will unblind the study for the purpose of the Week 24 analysis; however, subjects and investigators will remain blinded to treatment allocation until each subject has reached their Week 96 visit. The Week 24 analysis will be used for regulatory purposes and no external presentation of the data will occur until at least all patients have reached the Week 48 visit (when the primary analysis will occur).

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 and sister study 205543. 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. Further, an interim futility analysis will be performed for the IDMC to evaluate the efficacy and safety of DTG plus 3TC when approximately 50% of subjects have completed their visit at Week 24; the sponsor will remain blinded to this analysis. Full details of the methods, timing, decision criteria and operating characteristics will be pre-specified in the IDMC Charter.

9.4. Key Elements of Analysis Plan

9.4.1. Efficacy Analyses

For the primary comparison, adjusted estimates of the difference in the rate of responders between the two arms will be presented along with CIs based on a stratified analysis using Cochran-Mantel-Haenszel (CMH) weights. All CIs will be two-sided. For the statistical analysis, four strata (subgroups) will be formed according to the combinations of levels of the following categorical variables:

- Baseline plasma HIV-1 RNA (≤ vs.>100,000c/mL);
- Baseline CD4+ cell count (≤ vs. >200 cells/mm^3).

The CMH estimate of the common difference in rates across strata will be calculated as the weighted average of the strata-specific estimates of the difference in response rates between the two arms as follows.

If n_k is the number of DTG plus 3TC treated subjects, m_k is the number of DTG plus TDF/FTC treated subjects, and $N_k = n_k + m_k$ is the total number of subjects in the k^{th} stratum, then the CMH estimate is given by

$$\hat{d}_{cmh} = \frac{\sum W_k \hat{d}_k}{\sum W_k}$$

where

$$W_k = \frac{n_k m_k}{N_k}$$

are CMH weights and $\hat{d}_k$ are estimates of the differences in response rates between the two treatment arms, $r_d - r_f$, for the k^{th} strata.

The corresponding two-sided 95% CI will be calculated as

$$\hat{d}_{cmh} \pm 1.96 \times \sqrt{\widehat{var}(\hat{d}_{cmh})}$$

using the variance estimator $\widehat{var}(\hat{d}_{cmh})$ given by [Sato, 1989] which is consistent in both sparse data and large strata. The full equation for this variance estimate is provided in the RAP. Full details will be contained in the RAP.

The weighted least squares chi-squared statistic [Fleiss, 1981] will be used to test for one-way homogeneity across the levels of each categorical variable, with each categorical variable considered separately. Following Lui and Kelly [Lui, 2000], ½ will be added to each cell in any strata for which the stratum-specific rate estimates of either r_d or r_f are zero, and tests will be one-sided. Any heterogeneity found to be statistically significant will be explored and if necessary results will be reported for each level of the categorical variable. Investigation of heterogeneity will be confined to the primary endpoint using the Week 24 and Week 48 Snapshot analyses. Tests of homogeneity will be assessed at the one-sided 10% level of significance.

A sensitivity analysis will be performed at Week 48 to assess whether bias was introduced by the unblinded analysis performed at Week 24. The Week 48 Snapshot results of the subjects who reached Week 48 prior to the Week 24 unblinding will be compared to the Week 48 results in the subjects who reached Week 48 after the Week 24 unblinding.

Further efficacy analyses to assess the sensitivity of the primary endpoint will be performed. Details of the sensitivity analyses will be included in the RAP and will include 'time to event' methods which censor subjects who discontinue from the study with viral load <50 c/ml or for non-efficacy-treatment related reasons. In these analyses, subjects will be considered to have had an event if they have a confirmed viral load ≥50 c/ml or discontinue for efficacy-related reasons.

The incidence of HIV-1 disease progression (AIDS and death) will be presented. The proportion of subjects with plasma HIV-1 RNA <50 c/mL and changes from baseline in CD4+ cell count will be summarised by subgroups (e.g. age, gender, race, baseline CD4+ cell counts).

Details for secondary efficacy endpoints will be discussed in the RAP.

Data gathered after subjects withdraw from study treatment will be listed but will not be included in summary tables. Data will be allocated to visit windows using actual visit dates rather than nominal visit numbers. Data collected from extra visits within a window will be listed and will be included in the derivation of the Snapshot response at analysis visits of interest, but summary tables using OC datasets will only use the data captured closest to the target visit date. Detailed explanations of the derivation of visit windows will be included in the RAP. Any deviations from planned analyses will be detailed in the clinical study report (CSR).

9.4.2. Safety Analyses

The observed case dataset will be the primary dataset used for analysis of safety endpoints.

Exposure to study medication, measured by the number of weeks on study drug, will be summarised by treatment group. The proportion of subjects reporting AEs will be tabulated for each treatment group. 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; and
- Incidence of SAEs.

Statistical analysis of selected biomarkers and fasting lipids may be performed overall and by baseline demographics using appropriate methods for missing data. Further details will be provided in the RAP.

Laboratory, biomarker and vital signs data will be summarised by visit and treatment group. In addition, the number and percentage of subjects with graded laboratory toxicities (based on DAIDS categories; Appendix 6, Section 12.6) will be summarised by treatment group. The proportion of subjects experiencing changes from Baseline in their National Cholesterol Education Program (NCEP) lipid categories will be summarised by treatment arm. Further details of safety analyses will be included in the RAP.

9.4.3. Viral Genotyping/Phenotyping Analyses

The incidence of treatment-emergent genotypic and phenotypic resistance to DTG, 3TC and TDF/FTC will be summarised by treatment arm for subjects meeting CVW criteria (Section 5.4.1). Details of the analyses to be performed will be specified in the RAP.

9.4.4. Other Analyses

The change from Baseline in health related quality of life using EQ-5D-5L will be summarised as detailed in Section 7.7.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. 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 subjects begins.

10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a site, ViiV Healthcare/GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements, and with ViiV Healthcare/GSK policy.

The study will also be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable;
- Obtaining signed informed consent;
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC).

ViiV Healthcare/GSK/PPD will provide full details of the above procedures, either verbally, in writing, or both.

Signed informed consent must be obtained for each subject (or his/her legal representative) prior to participation in the study (and for amendments as applicable).

10.3. Quality Control (Study Monitoring)

- 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 subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents

10.4. Quality Assurance

- 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.

10.5. 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 temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicentre studies, this can occur at one or more or at all sites.
- If ViiV Healthcare/GSK determines such action is needed, ViiV Healthcare/GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, ViiV Healthcare/GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, ViiV Healthcare/GSK/PPD will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. ViiV Healthcare/GSK/PPD will also promptly inform the relevant regulatory authorities of

the suspension or premature discontinuation of the study and the reason(s) for the action.

- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. 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.
- The Investigator's Site Files must be retained for 25 years from the date of the final CSR. ViiV Healthcare, GSK or PPD will inform the investigator of the retention period due date at the time when this CSR (or equivalent) is issued to the site.
- 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.

10.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

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 subjects, as appropriate.

ViiV Healthcare/GSK will provide the investigators with the randomisation codes for their sites only after completion of the full statistical analysis.

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.

10.8. Independent Data Monitoring Committee

An IDMC will be utilised 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 subjects and to protect the scientific validity of this study and sister study 205543. The schedule of any planned interim analysis and the analysis plan for IDMC review is described in the 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.

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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
B2M	Beta-2 Microglobulin
BMI	Body mass index
c/mL	Copies/millilitre
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMH	Cochran-Mantel-Haenszel
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CrCl	Creatinine clearance
CRF	Case report form
CSR	Clinical study report
C-SSRS	Columbia Suicidality Severity Rating Scale
CV	Cardiovascular
CVW	Confirmed Virologic Withdrawal
DAIDS	Division of Acquired Immunodeficiency Syndrome
DILI	Drug induced liver injury
DNA	Deoxyribonucleic acid
DRV	Darunavir
DTG	Dolutegravir, TIVICAY
ECG	Electrocardiogram
eCRF	Electronic case report form
eC-SSRS	Electronic Columbia Suicidality Severity Rating Scale
EFV	Efavirenz
EQ-5D-5L	EuroQol – 5 Dimensions – 5 Levels
EU	European Union
FDA	Food and Drug Administration
FDC	Fixed-dose combination
FRP	Females of Reproductive Potential
FSH	Follicle stimulating hormone
FTC	Emtricitabine

GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GFR	Glomerular filtration rate
GSK	GlaxoSmithKline
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	Human chorionic gonadotrophin
HCV	Hepatitis C virus
HDL	High density lipoprotein
HDPE	High density polyethylene
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HPMC	Hydroxypropyl methylcellulose
HRT	Hormone replacement therapy
HSR	Hypersensitivity reaction
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
INR	International normalised ratio
INSTI	Integrase strand transfer inhibitor
IP	Investigational Product
IRB	Institutional Review Board
ITT-E	Intent-to-treat exposed
IVRS	Interactive voice recognition system
IWRS	Interactive web recognition system
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LPV	Lopinavir
MCH	Mean corpuscular haemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
mg	Milligram
mg/dL	Milligram per decilitre
MSD=F	Missing, switch, or discontinuation equals failure
MSDS	Material Safety Data Sheet
NCEP	National Cholesterol Education Program
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
OC	Observed case
OCT2	Organic cation transporter 2
PBMC	Peripheral blood mononuclear cell
PEP	Post-exposure prophylaxis
PI	Protease inhibitor
PK	Pharmacokinetic(s)
PP	Per-protocol

PPD	Pharmaceutical Product Development
PrEP	Pre-exposure prophylaxis
PRO	Protease
PRTD	Proximal Renal Tubule Dysfunction
PSRAE	Possible suicidality-related adverse event
RAL	Raltegravir
RAP	Reporting and Analysis Plan
RBC	Red blood cell
RBP	Retinol Binding Protein
RNA	Ribonucleic acid
RPR	Rapid plasma reagin
RT	Reverse transcriptase
RTV	Ritonavir
SAE	Serious adverse event
SJS	Stevens-Johnson syndrome
SRM	Study Reference Manual
STR	Single tablet regimen
SVW	Suspected Virologic Withdrawal
TDF	Tenofovir disoproxil fumarate
TEN	Toxic epidermal necrolysis
TRDF	Treatment Related Discontinuation = Failure
ULN	Upper limit of normal
US	United States
VAS	Visual analogue scale
VSLC	ViiV Healthcare Safety and Labelling Committee
WBC	White blood cell
ZDV	Zidovudine, RETROVIR
ZDV/3TC	Zidovudine/lamivudine, COMBIVIR

Trademark Information

Trademarks of ViiV Healthcare
COMBIVIR
EPIVIR
EPZICOM/KIVEXA
RETROVIR
TIVICAY
ZIAGEN

Trademarks not owned by ViiV Healthcare
Abbott RealTime
GenoSure
Monogram Biosciences
PhenoSense
Q^2 Solutions
Truvada

12.2. Appendix 2: Child-Pugh Classification

A subject is classified with mild hepatic impairment (Class A) if their overall sum of scores is 5-6 points, moderate hepatic impairment (Class B) if their overall sum of scores is 7-9 points, and severe hepatic impairment (Class C) if their overall sum of scores is 10-15 based on the Child-Pugh system [Pugh, 1973] scoring described in the following table (Table 3). For subjects requiring anticoagulation therapy, discussion with the study Medical Monitor will be required.

Table 3 Child-Pugh System

Finding	Points Scored for Each Observed Finding		
	1	2	3
Encephalopathy Grade[1]	None	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Serum bilirubin, SI units (μmol/L), Serum bilirubin, conventional units (mg/dL)	<34 <2	34 to 52 2 to 3	>52 >3
Serum albumin, SI units (g/L) Serum albumin, conventional units (mg/dL)	>35 >3.5	28 to 35 2.8 to 3.5	<28 <2.8
Prothrombin Time (seconds prolonged) or INR	<4 <1.7	4 to 6 1.7 to 2.3	>6 >2.3

1. Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles per second waves
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4: unrousable coma, no personality/behaviour, decerebrate, slow 2-3 cycles per second delta activity
[Pugh, 1973; Lucey, 1997]

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

Liver Chemistry Stopping Criteria - Liver Stopping Event	
ALT-absolute	ALT ≥ 8xULN
ALT Increase	ALT ≥ 5xULN but <8xULN persists for ≥2 weeks (with bilirubin <2xULN and no signs or symptoms of acute hepatitis or hypersensitivity)
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
Cannot Monitor	ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for >2 weeks
Symptomatic[3]	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

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**

• Immediately discontinue study treatment.
• Report the event to the Medical Monitor **within 24 hours**.
• Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2].
• Complete the liver imaging and/or liver biopsy eCRFs if these tests are performed.
• Perform liver event follow up assessments.
• Monitor the subject until liver chemistries resolve, stabilise, or return to within baseline (see **MONITORING** below).
• **Do not restart** subject with study treatment unless allowed per protocol and VSLC approval **is granted** (refer to Appendix 4).
• If restart is **not allowed or not granted**, permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments.
	Make every attempt to carry out liver event follow-up assessments at the central laboratory as described below:
	• 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.
	• Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen

MONITORING: • Make every reasonable attempt to have subjects return to clinic within **24 hours** for repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments. • Monitor subjects twice weekly until liver chemistries resolve, stabilise or return to within baseline. • A specialist or hepatology consultation is recommended.	contribution to liver injury in subjects 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 computerised 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. • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake CRF.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject 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 subjects 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 CRF. If the date or time of the last dose is unclear, provide the subject'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 SRM.

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 subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until resolution or stabilisation (ALT <5×ULN on 2 consecutive evaluations) • If at any time subject meets the liver chemistry stopping criteria, proceed as described above

Reference

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12.4. Appendix 4: Liver Safety – Study Treatment Restart Guidelines

VSLC GUIDELINES FOR DRUG RESTART AFTER STOPPING FOR LIVER CRITERIA

In Phase III, **drug restart** may be considered for liver events with a clear underlying cause (e.g., biliary, pancreatic events, hypotension, acute viral hepatitis), if not associated with drug-induced liver injury, alcoholic hepatitis or hypersensitivity, and drug not associated with human leukocyte antigen (HLA) marker of liver injury, when liver chemistries improve to within 1.5x baseline and ALT<3xULN) (Table 4, Figure 3).

Drug Restart

Phase III "drug restart" can be approved by the VSLC for **transient, defined non-drug-induced liver injury if no evidence of:**

- immunoallergic injury /HLA association with injury
- drug-induced liver injury (DILI)
- alcoholic hepatitis

Study drug is held while labs and evaluation is completed to assess diagnosis.

VSLC Decision Process for Drug Restart Approval or Disapproval (Figure 3):

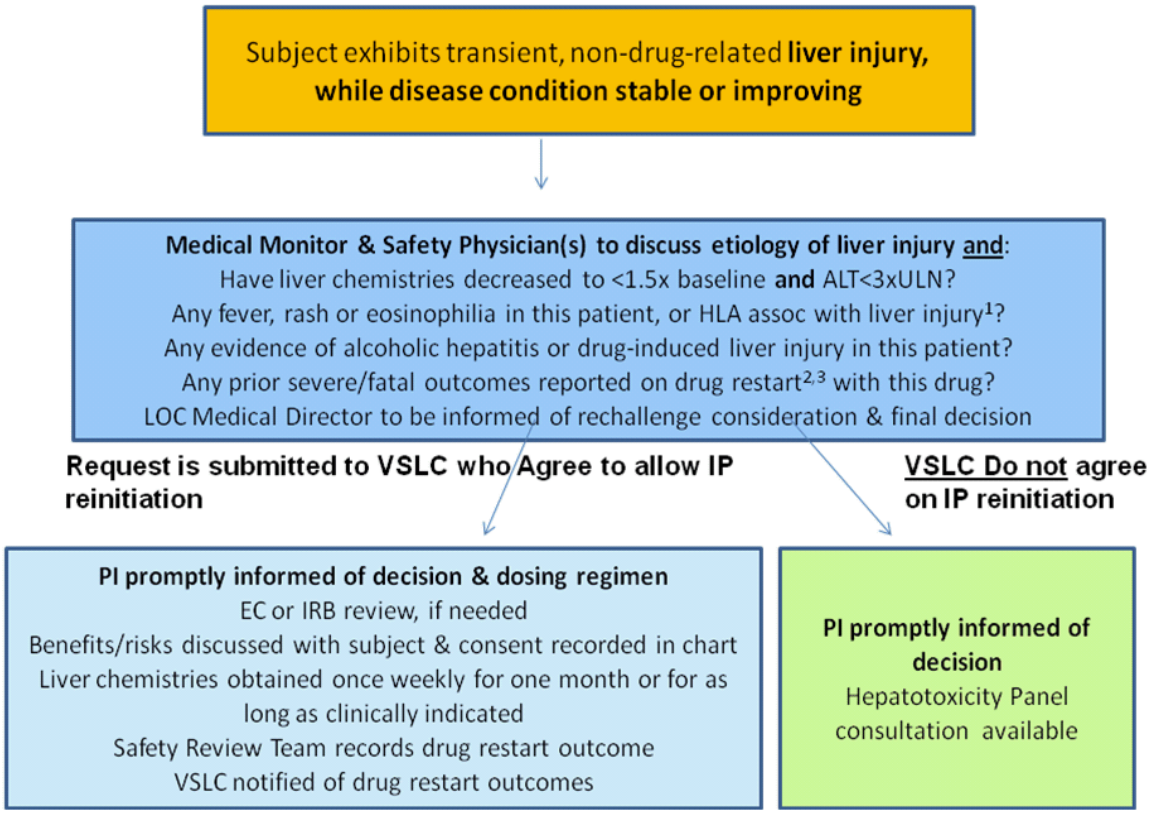
- PI requests consideration of drug re-initiation for a subject stable or improving on study drug, who exhibits liver chemistry elevation meeting subject stopping criteria, which is transient, non-drug-related, and liver chemistries improve to within 1.5x baseline and ALT< 3xULN.
- Medical monitor and Clinical Safety Physician to review the subject's diagnosis, restart risk factors and complete checklist (Table 4).
  - The LOC medical director (ViiV Healthcare and GSK where applicable) should be informed that study drug restart is under consideration and of the final decision, whether or not to proceed.

Table 4 Checklist for Phase III drug restart after well-explained liver injury (e.g., biliary, pancreatic, hypotensive events, congestive heart failure, acute viral hepatitis), improving to liver chem.≤1.5x baseline & ALT<3xULN

	Yes	No
Was subject stable or improving on study drug?		
Do not restart if the **following risk factors at initial liver injury**:		
• fever, rash, eosinophilia, or hypersensitivity		
• drug-induced liver injury		
• alcoholic hepatitis (AST>ALT, typically <10xULN)		
• study drug has an HLA genetic marker associated with liver injury (e.g., lapatinib, abacavir, amoxicillin/clavulanate)		
Previous drug history		

- Relevant physicians must review and agree on request for drug restart:
  - Safety Team Leader, VP, or Senior Safety Physician
  - Medicines Development Leader and Project Physician Leader.
- Hepatotoxicity Panel consultation is available.
- Justification for drug restart outlining the benefit and risk for this subject must be recorded by GCSP Physician and sent to the VSLC Secretary.
  - VSLC must approve drug re-initiation and dosing regimen

Figure 3 VSLC process for drug restart approval or disapproval



1. Andrade, 2009; 2. Papay, 2009; 3. Hunt, 2010

Medical Monitor, GCSP Physician and PI actions for Restart following VSLC decision

Medical Monitor and (Global Clinical Safety and Pharmacovigilance) GCSP Physician Actions

- Medical Monitor must notify PI of VSLC's restart decision and recommended dosing regimen in writing and Medical Monitor must record note in study files.
- The Safety Review Team must record restart outcomes and the GCSP Physician must send these to the VSLC
  - All severe reactions (restart associated with bilirubin>2xULN or jaundice, or INR≥1.5), SAEs or fatalities with drug restart must be immediately reported to Line Management, VSLC Chair, VP Global Medical Strategy and EU Qualified Person for Pharmacovigilance.

Principal Investigator Actions:

- The PI must obtain Ethics Committee or Institutional Review Board approval of drug restart, as required.
- If drug re-initiation VSLC-approved, the patient must provide informed consent with a clear description of possible benefits and risks of drug administration including recurrent, more severe liver injury or possible death.
- The patient's informed consent must be recorded in the study chart, and the drug administered at agreed dose, as communicated by Medical Monitor.
- Liver chemistries must be followed ***once weekly for 'restart' cases*** for one month or for as long as clinically indicated following drug re-initiation. If subject exhibits protocol-defined liver chemistry elevations, study drug should be discontinued as protocol specified.

VSLC and the IRB/IEC must be informed of the patient's outcome following drug restart.

Restart safety outcomes:

- 0 = no liver chemistry elevation
- 1 = recurrent liver chemistry elevation not meeting subject stopping criteria
- 2 = recurrent liver chemistry elevation meeting subject stopping criteria
- 3 = serious adverse event
- 4 = fatality

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, et al. Drug-induced liver injury following positive drug rechallenge. Regul Tox Pharm. 2009; 54:84-90.

12.5. Appendix 5: CDC Classification for HIV-1 Infection (2014)

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.

Stage 3-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

CDC. Revised Surveillance Case Definition for HIV Infection – United States, 2014. MMWR 2014; 63 (RR-03);1-10.

12.6. Appendix 6: Division of AIDS table for Grading Severity of Adult and Pediatric Adverse Events

VERSION 2.0, November 2014

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 utilised for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical adverse event **NOT** identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

Major Clinical Conditions

Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arrhythmia (by ECG or physical examination) *Specify type, if applicable*	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Blood Pressure Abnormalities[1] ***Hypertension*** *(with the lowest reading taken after repeat testing during a visit)* *≥ 18 years of age*	140 to < 160 mmHg systolic OR 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
< 18 years of age	> 120/80 mmHg	≥ 95th to < 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥ 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Cardiac Ischemia or Infarction *Report only one*	NA	NA	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR Intervention indicated (e.g., oxygen)	Life-threatening consequences OR Urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)
Hemorrhage (with significant acute blood loss)	NA	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤ 2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children, packed RBCs > 10 cc/kg) indicated
Prolonged PR Interval or AV Block *Report only one* *> 16 years of age*	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
≤ 16 years of age	1st degree AV block (PR interval > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
Prolonged QTc Interval[2]	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds OR ≥ 0.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism *Report only one*	NA	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)

[1] Blood pressure norms for children < 18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. Pediatrics 2011;128;S213; originally published online November 14, 2011; DOI: 10.1542/peds.2009-2107C.
[2] As per Bazett's formula.

Dermatologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one	Generalized	NA
Pruritus[3] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis

[3] For pruritus associated with injections or infusions, see the Site Reactions to Injections and Infusions section.

Endocrine and Metabolic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma, end organ failure)
Gynecomastia	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Lipoatrophy[4]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA
Lipohypertrophy[5]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

[4] Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.
[5] Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen.

Gastrointestinal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequencs
Bloating or Distension *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea *≥ 1 year of age*	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
< 1 year of age	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Life-threatening consequences (e.g., liquid stools resulting in severe dehydration, hypotensive shock)
Dysphagia or Odynophagia *Report only one and specify location*	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)
Mucositis or Stomatitis **Report only one and specify location**	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous mucosal bleeding
Nausea	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Perforation (colon or rectum)	NA	NA	Intervention indicated	Life-threatening consequences

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NA	NA
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)

Musculoskeletal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arthralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	No symptoms but with radiographic findings AND No operative intervention indicated	Bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
Osteopenia[6] *≥ 30 years of age*	BMD t-score -2.5 to -1	NA	NA	NA
< 30 years of age	BMD z-score -2 to -1	NA	NA	NA
Osteoporosis[6] *≥ 30 years of age*	NA	BMD t-score < -2.5	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
< 30 years of age	NA	BMD z-score < -2	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences

[6] BMD t and z scores can be found in: Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield.

Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute CNS Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
Altered Mental Status (for Dementia, see *Cognitive, Behavioral, or Attentional Disturbance* below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR Obtundation OR Coma
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, Behavioral, or Attentional Disturbance (includes dementia and attention deficit disorder) *Specify type, if applicable*	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part- time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full- time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Developmental Delay *< 18 years of age* *Specify type, if applicable*	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function
Neuromuscular Weakness (includes myopathy and neuropathy) **Specify type, if applicable**	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation

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

Pregnancy, Puerperium, and Perinatal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Fetal Death or Stillbirth (report using mother's participant ID) *Report only one*	NA	NA	Fetal loss occurring at ≥ 20 weeks gestation	NA
Preterm Delivery[7] (report using mother's participant ID)	Delivery at 34 to < 37 weeks gestational age	Delivery at 28 to < 34 weeks gestational age	Delivery at 24 to < 28 weeks gestational age	Delivery at < 24 weeks gestational age
Spontaneous Abortion or Miscarriage[8] (report using mother's participant ID) *Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA

[7] Definition: A delivery of a live-born neonate occurring at ≥ 20 to < 37 weeks gestational age.
[8] Definition: A clinically recognized pregnancy occurring at < 20 weeks gestational age.

Psychiatric

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early	Moderate difficulty falling asleep, staying asleep, or waking up early	Severe difficulty falling asleep, staying asleep, or waking up early	NA
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) *Specify disorder*	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions
Suicidal Ideation or Attempt *Report only one*	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated	Suicide attempted

Respiratory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥ 70 to < 80% OR Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50 to < 70% OR Symptoms with intervention indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Forced expiratory volume in 1 second or peak flow 25 to < 50% OR Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow < 25% OR Life-threatening respiratory or hemodynamic compromise OR Intubation
Dyspnea or Respiratory Distress *Report only one*	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 to < 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)

Sensory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hearing Loss *≥ 12 years of age*	NA	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (> 80 dB at 2 kHz and above) OR Non-serviceable hearing (i.e., >50 dB audiogram and <50% speech discrimination)
< 12 years of age (based on a 1, 2, 3, 4, 6 and 8 kHz audiogram)	> 20 dB hearing loss at ≤ 4 kHz	> 20 dB hearing loss at > 4 kHz	> 20 dB hearing loss at ≥ 3 kHz in one ear with additional speech language related services indicated (where available) OR Hearing loss sufficient to indicate therapeutic intervention, including hearing aids	Audiologic indication for cochlear implant and additional speech-language related services indicated (where available)
Tinnitus	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	NA
Uveitis	No symptoms AND Detectable on examination	Anterior uveitis with symptoms OR Medicamylasal intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions
Visual Changes (assessed from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

Systemic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Cytokine Release Syndrome[9]	Mild signs and symptoms AND Therapy (i.e., antibody infusion) interruption not indicated	Therapy (i.e., antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤ 24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Fatigue or Malaise *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0 to < 38.6°C or 100.4 to < 101.5°F	≥ 38.6 to < 39.3°C or ≥ 101.5 to < 102.7°F	≥ 39.3 to < 40.0°C or ≥ 102.7 to < 104.0°F	≥ 40.0°C or ≥ 104.0°F
Pain[10] (not associated with study agent injections and not specified elsewhere) *Specify location*	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated
Serum Sickness[11]	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (e.g., antihistamines)	Severe signs and symptoms AND Higher level intervention indicated (e.g., steroids or IV fluids)	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Underweight[12] *> 5 to 19 years of age*	NA	WHO BMI z-score < -2 to ≤ -3	WHO BMI z-score < -3	WHO BMI z-score < -3 with life-threatening consequences

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
2 to 5 years of age	NA	WHO Weight-for-height z-score < -2 to ≤ -3	WHO Weight-for-height z-score < -3	WHO Weight-for-height z-score < -3 with life- threatening consequences
< 2 years of age	NA	WHO Weight-for-length z-score < -2 to ≤ -3	WHO Weight-for-length z-score < -3	WHO Weight-for-length z-score < -3 with life- threatening consequences
Weight Loss (excludes postpartum weight loss)	NA	5 to < 9% loss in body weight from baseline	≥ 9 to < 20% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)

[9] Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.
[10] For pain associated with injections or infusions, see the Site Reactions to Injections and Infusions section.
[11] Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.
[12] WHO reference tables may be accesed by clicking the desired age range or by accessing the following URLs: http://www.who.int/growthref/who2007_bmi_for_age/en / for participants > 5 to 19 years of age and http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those ≤ 5 years of age.

Urinary

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Urinary Tract Obstruction	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life- threatening consequences

Site Reactions to Injections and Infusions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Injection Site Pain or Tenderness *Report only one*	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or Redness[13] *Report only one* *> 15 years of age*	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter OR ≥ 100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
≤ 15 years of age	≤ 2.5 cm in diameter	> 2.5 cm in diameter with < 50% surface area of the extremity segment involved (e.g., upper arm or thigh)	≥ 50% surface area of the extremity segment involved (e.g., upper arm or thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling *Report only one* *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
≤ 15 years of age	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in < 48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

[13] Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.

Laboratory Values

Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acidosis	NA	pH ≥ 7.3 to < LLN	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to < LLN *30 to < LLN*	≥ 2.0 to < 3.0 *≥ 20 to < 30*	< 2.0 *< 20*	NA
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Alkalosis	NA	pH > ULN to ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT or SGPT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Creatine Kinase, High	3 to < 6 x ULN	6 to < 10 x ULN	10 to < 20 x ULN	≥ 20 x ULN
Creatinine, High	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase of > 0.3 mg/dL above baseline	> 1.8 to < 3.5 x ULN OR Increase of 1.5 to < 2.0 x above baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x above baseline
Creatinine Clearance 15 or eGFR, Low *Report only one*	NA	< 90 to 60 ml/min or ml/min/1.73 m^2 OR 10 to < 30% decrease from baseline	< 60 to 30 ml/min or ml/min/1.73 m2 OR ≥ 30 to < 50% decrease from baseline	< 30 ml/min or ml/min/1.73 m2 OR ≥ 50% decrease from baseline or dialysis needed
Glucose (mg/dL*; mmol/L)*				
Fasting, High	110 to 125 *6.11 to < 6.95*	> 125 to 250 *6.95 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	> 500 *≥ 27.75*
Nonfasting, High	116 to 160 *6.44 to < 8.89*	> 160 to 250 *8.89 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	> 500 *≥ 27.75*
Glucose, Low (mg/dL*; mmol/L)*				
≥ 1 month of age	55 to 64 *3.05 to 3.55*	40 to < 55 *2.22 to < 3.05*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
< 1 month of age	50 to 54 *2.78 to 3.00*	40 to < 50 *2.22 to < 2.78*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
Lactate, High	ULN to < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences
Lipase, High	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
Lipid Disorders (mg/dL*; mmol/L)*				
Cholesterol, Fasting, High				
≥ 18 years of age	200 to < 240 *5.18 to < 6.19*	240 to < 300 *6.19 to < 7.77*	≥ 300 *≥ 7.77*	NA
< 18 years of age	170 to < 200 4.40 to < 5.15	200 to < 300 5.15 to < 7.77	≥ 300 ≥ 7.77	NA
LDL, Fasting, High	130 to < 160	160 to < 190	≥ 190	NA

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
≥ 18 years of age	*3.37 to < 4.12*	*4.12 to < 4.90*	*≥ 4.90*	
> 2 to < 18 years of age	110 to < 130 *2.85 to < 3.34*	130 to < 190 *3.34 to < 4.90*	≥ 190 *≥ 4.90*	NA
Triglycerides, Fasting, High	150 to 300 *1.71 to 3.42*	>300 to 500 *>3.42 to 5.7*	>500 to < 1,000 *>5.7 to 11.4*	> 1,000 *> 11.4*
Magnesium[16], Low (mEq/L*; mmol/L)*	1.2 to < 1.4 *0.60 to < 0.70*	0.9 to < 1.2 *0.45 to < 0.60*	0.6 to < 0.9 *0.30 to < 0.45*	< 0.6 *< 0.30*
Phosphate, Low (mg/dL*; mmol/L)*				
> 14 years of age	2.0 to < LLN *0.81 to < LLN*	1.4 to < 2.0 *0.65 to < 0.81*	1.0 to < 1.4 *0.32 to < 0.65*	< 1.0 *< 0.32*
1 to 14 years of age	3.0 to < 3.5 *0.97 to < 1.13*	2.5 to < 3.0 *0.81 to < 0.97*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
< 1 year of age	3.5 to < 4.5 *1.13 to < 1.45*	2.5 to < 3.5 *0.81 to < 1.13*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
Potassium, High (mEq/L*; mmol/L)*	5.6 to < 6.0 *5.6 to < 6.0*	6.0 to < 6.5 *6.0 to < 6.5*	6.5 to < 7.0 *6.5 to < 7.0*	≥ 7.0 *≥ 7.0*
Potassium, Low (mEq/L*; mmol/L)*	3.0 to < 3.4 *3.0 to < 3.4*	2.5 to < 3.0 *2.5 to < 3.0*	2.0 to < 2.5 *2.0 to < 2.5*	< 2.0 *< 2.0*
Sodium, High (mEq/L*; mmol/L)*	146 to < 150 *146 to < 150*	150 to < 154 *150 to < 154*	154 to < 160 *154 to < 160*	≥ 160 *≥ 160*
Sodium, Low (mEq/L*; mmol/L)*	130 to < 135 *130 to < 135*	125 to < 130 *125 to < 135*	121 to < 125 *121 to < 125*	≤ 120 *≤ 120*
Uric Acid, High (mg/dL*; mmol/L)*	7.5 to < 10.0 *0.45 to < 0.59*	10.0 to < 12.0 *0.59 to < 0.71*	12.0 to < 15.0 *0.71 to < 0.89*	≥ 15.0 *≥ 0.89*

[14]Direct bilirubin > 1.5 mg/dL in a participant < 28 days of age should be graded as grade 2, if < 10% of the total bilirubin.
[15]Use the applicable formula (i.e., Cockroft-Gault in mL/min or Schwatrz in mL/min/1.73m^2).
[16]To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.

Haematology

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Absolute CD4+ Count, Low (cell/mm^3; *cells/L*) *> 5 years of age (not HIV infected)*	300 to < 400 *300 to < 400*	200 to < 300 *200 to < 300*	100 to < 200 *100 to < 200*	< 100 *< 100*
Absolute Lymphocyte Count, Low (cell/mm^3; *cells/L*) *> 5 years of age (not HIV infected)*	600 to < 650 *0.600 x 10^9 to < 0.650 x 10^9*	500 to < 600 *0.500 x 10^9 to < 0.600 x 10^9*	350 to < 500 *0.350 x 10^9 to < 0.500 x 10^9*	< 350 *< 0.350 x 10^9*
Absolute Neutrophil Count (ANC), Low (cells/mm^3; *cells/L*) *> 7 days of*	800 to 1,000 *0.800 x 10^9 to 1.000 x 10^9*	600 to 799 *0.600 x 10^9 to 0.799 x10^9*	400 to 599 *0.400 x 10^9 to 0.599 x10^9*	< 400 *< 0.400 x 10^9*
2 to 7 days of age	1,250 to 1,500 *1.250 x 10^9 to 1.500 x 10^9*	1,000 to 1,249 *1.000 x 10^9 to 1.249 x10^9*	750 to 999 *0.750 x 10^9 to 0.999 x10^9*	< 750 *< 0.750 x 10^9*
≤ 1 day of age	4,000 to 5,000 *4.000 x 109 to 5.000 x 10^9*	3,000 to 3,999 *3.000 x 10^9 to 3.999 x10^9*	1,500 to 2,999 *1.500 x 10^9 to 2.999 x10^9*	< 1,500 *< 1.500 x 10^9*
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to < 200 *1.00 to < 2.00* OR 0.75 to < 1.00 x LLN	75 to < 100 *0.75 to < 1.00* OR ≥ 0.50 to < 0.75 x LLN	50 to < 75 *0.50 to < 0.75* OR 0.25 to < 0.50 x LLN	< 50 *< 0.50* OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin[17], Low (g/dL; *mmol/L*)[18] *≥ 13 years of age (male only)*	10.0 to 10.9 *6.19 to 6.76*	9.0 to < 10.0 *5.57 to < 6.19*	7.0 to < 9.0 *4.34 to < 5.57*	< 7.0 *< 4.34*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
≥ 13 years of age (female only)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
57 days of age to < 13 years of age (male and female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
36 to 56 days of age (male and female)	8.5 to 9.6 *5.26 to 5.99*	7.0 to < 8.5 *4.32 to < 5.26*	6.0 to < 7.0 *3.72 to < 4.32*	< 6.0 *< 3.72*
22 to 35 days of age (male and female)	9.5 to 11.0 *5.88 to 6.86*	8.0 to < 9.5 *4.94 to < 5.88*	6.7 to < 8.0 *4.15 to < 4.94*	< 6.7 *< 4.15*
8 to ≤ 21 days of age (male and female)	11.0 to 13.0 *6.81 to 8.10*	9.0 to < 11.0 *5.57 to < 6.81*	8.0 to < 9.0 *4.96 to < 5.57*	< 8.0 *< 4.96*
≤ 7 days of age (male and female)	13.0 to 14.0 *8.05 to 8.72*	10.0 to < 13.0 *6.19 to < 8.05*	9.0 to < 10.0 *5.59 to < 6.19*	< 9.0 *< 5.59*
INR, High (not on anticoagulation therapy)	1.1 to < 1.5 x ULN	1.5 to < 2.0 x ULN	2.0 to < 3.0 x ULN	≥ 3.0 x ULN
Methemoglobin (% hemoglobin)	5.0 to < 10.0%	10.0 to < 15.0%	15.0 to < 20.0%	≥ 20.0%
PTT, High (not on anticoagulation	1.1 to < 1.66 x ULN	1.66 to < 2.33 x ULN	2.33 to < 3.00 x ULN	≥ 3.00 x ULN
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to < 124,999 *100.000 x 10^9 to < 124.999 x 10^9*	50,000 to < 100,000 *50.000 x 10^9 to < 100.000 x 10^9*	25,000 to < 50,000 *25.000 x 10^9 to < 50.000 x 10^9*	< 25,000 *< 25.000 x 10^9*
PT, High (not on anticoagulation therapy)	1.1 to < 1.25 x ULN	1.25 to < 1.50 x ULN	1.50 to < 3.00 x ULN	≥ 3.00 x ULN
WBC, Decreased (cells/mm^3*; cells/L*) *> 7 days of age*	2,000 to 2,499 *2.000 x 10^9 to 2.499 x 10^9*	1,500 to 1,999 *1.500 x 10^9 to 1.999 x10^9*	1,000 to 1,499 *1.000 x 10^9 to 1.499 x10^9*	< 1,000 *< 1.000 x 10^9*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
≤ 7 days of age	5,500 to 6,999 *5.500 x 10^9 to 6.999 x 10^9*	4,000 to 5,499 *4.000 x 10^9 to 5.499 x 10^9*	2,500 to 3,999 *2.500 x 10^9 to 3.999 x10^9*	< 2,500 *< 2.500 x 10^9*

[17]Male and female sex are defined as sex at birth.
[18]The conversion factor used to convert g/dL to mmol/L is 0.6206 and is the most commonly used conversion factor. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using the appropriate conversion factor for the particular laboratory.

Urinalysis

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	NA
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to < 10 RBCs per high power field	≥ 10 RBCs per high power field	Gross, with or without clots OR With RBC casts OR Intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA

Reference

U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0. [November 2014]. Available from: http://rsc.tech-res.com/Document/safetyandpharmacovigilance/DAIDS_AE_GRADING_TABLE_v2_NOV2014.pdf (accessed 10 September 2015)

12.7. Appendix 7: Definition of and Procedures for Recording, Evaluating, Follow-up and Reporting of Adverse Events

12.7.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • 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 prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected 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 this is an intentional overdose taken with possible suicidal/self-harming intent. This 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. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

Events <u>NOT</u> meeting definition of an AE include:
• 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 subject'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 subject's

condition.

- Medical or surgical procedure (e.g. endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where 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.

12.7.2. Definition of Serious Adverse Events

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

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE:

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject 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 hospitalisation or prolongation of existing hospitalisation

NOTE:

- In general, hospitalisation signifies that the subject 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 out-patient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.
- Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity

NOTE:

- 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, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere 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 reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. • Examples of such events are 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 hospitalisation, or development of drug dependency or drug abuse
g. Is associated with liver injury <u>and</u> 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 subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

12.7.3. 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: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension

- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularisation

12.7.4. Sentinel Events

Sentinel Event Definition:

A sentinel event is a GSK-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. 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-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)

12.7.5. Recording of AEs and SAEs

AEs and SAE Recording:

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE/SAE in the CRF
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to

submission of to GSK.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

12.7.6. Evaluating AEs and SAEs

Assessment of Intensity:

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe will not be confused with an SAE. Severity is a category utilised for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- 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 the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence 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 natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in the determination of 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 when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event**

prior to the initial transmission of the SAE data to ViiV Healthcare/GSK/PPD.

- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs:

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

12.7.7. Reporting of SAEs and other events to ViiV Healthcare/GSK/PPD

Reporting of SAEs and other events to ViiV Healthcare/GSK/PPD:

- Primary mechanism for reporting SAEs to the Medical Monitor will be the electronic data collection tool.
- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it (or scan and email it) to the Medical Monitor.
- Site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE.
- After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) 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 subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical

Monitor by telephone.

- Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

	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	2 weeks	"Pregnancy Notification Form"	2 weeks	"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]
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 subject 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. Appendix 8: Toxicity Management

Adverse events that occur during the trial should be evaluated by the investigator and graded according to the DAIDS toxicity scales (see Section 12.6). Additional information regarding detecting, documenting and reporting AEs and SAEs are available in Section 12.7.

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 subject 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 subject's eCRF.

Grade 1 or Grade 2 Toxicity/Adverse Event

Subjects who develop a Grade 1 or Grade 2 AE or toxicity may continue study treatment at the discretion of the investigator. Subjects 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

Subjects 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.

Subjects 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 subject, study treatment should be permanently discontinued and the subject withdrawn from study. Subjects 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.

Subjects 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 12.8.1.7 and rash in Section 12.8.1.6.

Grade 4 Toxicity/Adverse Event

Subjects 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. Subjects should be rechecked each week until the AE returns to Grade 2.

Subjects 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.

Subjects 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 12.8.1.7. An in-clinic Follow-up visit will be conducted approximately 4 weeks after the last dose of study medication for subjects with ongoing AEs, and SAEs and also any laboratory abnormalities that are considered to be AEs or potentially harmful to the subject, at the last on-study visit.

12.8.1. 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.

Subjects 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 Appendix 7, Section 12.7.

12.8.1.1. Liver Chemistry Stopping and Follow-up Criteria

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event aetiology during administration of study drug and the follow-up period. For a complete listing of stopping and follow-up criteria refer to Appendix 3, Section 12.3.

12.8.1.2. Restarting Study Drug

Refer to Appendix 4, Section 12.4 for details on drug restart following transient resolving liver events not related to study treatment.

12.8.1.3. Decline in Renal Function

Subjects who experience an increase in serum creatinine from Baseline of 45 micromoles/litre (µMol/L) (or 0.5 milligrams/decilitre [mg/dL]) should return for a confirmatory assessment within 2 to 4 weeks. A urinalysis and urine albumin/creatinine and urine total protein/albumin ratios should also be done at this confirmatory visit. If the creatinine increase is confirmed, the investigator should contact the study Medical Monitor to discuss additional follow-up and medical management.

Subjects who experience progression to an estimated GFR (using the CKD-EPI method) of <50 mL/min/1.73 m^2 must return for a confirmatory assessment within 2 weeks [Levey, 2009]. A urinalysis and urine albumin/creatinine and urine protein/creatinine ratios should be done at this confirmatory visit. If an estimated GFR of <50 mL/min/1.73 m^2 is confirmed, then study treatment should be discontinued and the subject withdrawn from the study (as dose adjustment is needed for NRTIs, which is not possible in this blinded study).

Proximal Renal Tubule Dysfunction

Proximal Renal Tubule Dysfunction (PRTD) is defined as:

- Confirmed rise in serum creatinine of ≥0.5 mg/dL from Baseline AND serum phosphate <2.0 mg/dL;
- Either of the above accompanied by any two of the following:
- Glycosuria (≥250 mg/dL) in a non-diabetic;
- Low serum potassium (<3 mEq/L);
- Low serum bicarbonate (<19 mEq/L).

Subjects meeting criteria for PRTD must return for a confirmatory assessment within 2 weeks of diagnosis. A urinalysis should also be performed at the time of the confirmatory assessment. If PRTD is confirmed subjects must be withdrawn from the study.

12.8.1.4. Proteinuria

Subjects with an abnormal urine microalbumin/creatinine ratio (>0.3 mg/mg, >300 mg/g, or >34 mg/mmol) that represents a change from Baseline and no associated increase in creatinine, should have a repeat spot urine microalbumin/creatinine ratio performed within 2-4 weeks. If confirmed, then consideration should be given to additional evaluation after consultation with the study Medical Monitor. Additional evaluation may include a 24-hour urine protein and creatinine measurement and nephrology referral.

Subjects with an abnormal urine albumin/creatinine ratio (>0.3 mg/mg, 300 mg/g, or >34 mg/mmol and representing a change from Baseline) and a serum creatinine increase >45 µmol/L (or 0.5 mg/dL) should have confirmation of both results within 2 weeks. If confirmed, the study Medical Monitor should be contacted immediately. Agreement on further management should be agreed between the investigator and Medical Monitor.

12.8.1.5. Allergic reaction

Subjects may continue study drug for Grade 1 or 2 allergic reactions at the discretion of the Investigator. The subject 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.

Subjects 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 subject should be withdrawn from the study. Subjects should be treated as clinically appropriate and followed until resolution of the AE.

12.8.1.6. 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 RM2007/00683/09].

Subjects with an isolated Grade 1 rash may continue study drug at the Investigator's discretion. The subject 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.

Subjects 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 subject 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.

Subjects 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 subject should be withdrawn from the study. Subjects 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, Appendix 6, Section 12.6).

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.

12.8.1.7. Hypertriglyceridemia/Hypercholesterolemia

Samples for lipid measurements must be obtained in a fasted state according to the Time and Events Table (Section 7.1). Subjects who experience asymptomatic triglyceride or cholesterol elevations may continue to receive study drug.

12.8.1.8. 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 subject 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 subject withdrawn from the study.

References

GlaxoSmithKline Document Number RM2007/00683/09: GSK1349572 Clinical Investigator's Brochure, version 09. October 2015.

Levey AS, Stevens LA, Schmid CH, et.al. A new equation to estimate glomerular filtration rate. Ann Int Med. 2009; 150: 604-612.

12.9. Appendix 9: Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information

12.9.1. 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 subjects 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.

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 subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2011]. The documentation on male sterility can come from the site personnel's review of subject'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 subjects understand how to properly use these methods of contraception.

12.9.2. Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to ViiV Healthcare/GSK/PPD within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, 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.
- Any termination of pregnancy will be reported, regardless of foetal 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 the Medical Monitor as described in Appendix 7, Section 12.7. 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 subject 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, et al, editors. Contraceptive Technology. 20th edition. Atlanta, Georgia: Ardent Media, Inc., 2011: 50. Table 3-2.

12.10. Appendix 10: Country-specific Requirements

United Kingdom

This requirement has been included based on requests from the Medicines and Healthcare products Regulatory Agency (MHRA) to include information on the specific duration of the Continuation Phase/Study Treatment for similar Phase III trials being conducted with dolutegravir.

Study Duration

In this study, the date of last study treatment administration in the UK will be determined by the completion of the 148 week randomised phase of the study for the last UK subject enrolled (it will not be determined by the completion of the Continuation Phase). The last subject will be enrolled by March 2017, and hence the last study treatment administration will occur by January 2020. (Note: The Continuation Phase is intended to provide subjects randomised to DTG plus 3TC with post-study access to DTG plus 3TC until the DTG plus 3TC is approved as a dual regimen in their local countries. For subjects in the UK, the Continuation Phase is anticipated to conclude by December 2020, when the dual regimen of DTG plus 3TC is anticipated to be approved).