TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A Phase III, randomized, multicenter, parallel-group, non-inferiority study evaluating the efficacy, safety, and tolerability of switching to dolutegravir plus lamivudine in HIV 1 infected adults who are virologically suppressed

Compound Number: GSK1349572+GR109714 (GSK3515864)

Development Phase: III

Effective Date: 29-AUG-2018

Protocol Amendment Number: 06

Author (s): PPD

Copyright 2018 ViiV Healthcare group of companies. All rights reserved. Unauthorised copying or use of this information is prohibited.

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2015N242992_00	2017-FEB-27	Original
2015N242992_01	2017-MAY-16	Amendment No. 1
Tenofovir alafenamide (TAF) was corrected by removal of the word "fumarate". Clarification was provided in the overall design to specify that subjects randomized to TBR will switch to DTG + 3TC at Week 52 if HIV-1 RNA <50 c/mL at Week 48 (or upon retest by Week 52). Biomarkers of inflammation and mitochondrial function were removed as exploratory endpoints. A Week 96 endpoint was added to the measurement of biomarkers of telomerase function in a subset of subjects. Cardiovascular biomarker measurements were removed as exploratory endpoints. Inclusion Criteria #5 was edited for clarity. Section 6.2, Protocol Permitted Substitutions, added. The text defining the TBR comparators as investigational medicinal product was removed; TBR comparators will be provided in designated, specific countries only, as needed. The Time and Events Table was modified to clarify that whole blood samples may be utilized for virology and for telomere length measurements, and cryopreserved PBMCs will be used to evaluate telomerase activity. Updated version of Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (v2.1), March 2017, was provided in Section 12.9. Changes were made to the protocol text to reflect the addition of Country Specific requirements for Japan. Minor revisions were made to the text to correct errors and improve accuracy.		
2015N242992_02	2017-JUN-13	Amendment No. 2
The impetus for this protocol amendment was to update Appendix 5, Appendix 6 and Appendix 8 based on the ViiV Healthcare templates for these appendices which are appropriate for the HIV patient population. The prior versions of these appendices were based on a general GSK template and were not appropriate. During this process, other updates were made to the protocol which are summarized in Appendix 11.		
2015N242992_03	2017-AUG-24	Amendment No.3
Amended to include: Addition of CD8+ Lymphocyte assessments, addition of inflammatory biomarkers assessments as new exploratory endpoints, revision of the sample size based on updated estimates for the primary endpoint for the investigational arm, and minor clarifications and corrections of typographical errors.		

2015N242992_04	2017-DEC-07	Amendment No. 4
Amended to include pharmacokinetics assessments in the DTG/3TC FDC arm as exploratory endpoints; to update exclusion criterion 18 and remove its corresponding secondary endpoint no longer relevant; to add HbA1c and HOMA-IR assessments, For clarification purposes, the AE severity gradings in Appendix 8, Section 13.8.6 (Evaluating AEs and SAEs) were updated to be consistent with Appendix 9, Section 13.9. (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. Text was edited in Appendix 10, Section 13.10.2. to clarify wording for the country specific requirement for Japan.		
2015N242992_05	2018-JUN-14	Amendment No. 5
Changes were made to the protocol to manage and mitigate risks following identification of a potential safety issue related to neural tube defects in infants born to women with exposure to dolutegravir at the time of conception. Changes were also made to include updated text to address a higher number of participants screened than planned, to update references to the DTG IB to reflect the most current versions and to add clarification and correct minor typos. • The Risk Assessment table (Section 4.6.1) was updated to include language regarding risk and mitigation of neural tube defects. • The withdrawal criteria (Section 5.4) were updated to include a reminder that females of reproductive potential who change their minds and desire to be pregnant, or who state they no longer are willing to comply with the approved pregnancy avoidance methods, should also be withdrawn from the study. • The Time and Events table (Section 7.1). was updated to include a reminder for investigators to check at every visit that females of reproductive potential are avoiding pregnancy. • The modified list of highly effective methods for avoiding pregnancy in FRP (Section 13.3.1) was updated to exclude the double barrier method of contraception, which does not meet updated GSK/ViiV criteria for a highly effective method. • The Type and Number of Subjects (Section 4.3) and Sample Size Assumptions (Section 9.2.1) were updated to address a higher number of participants screened than planned.		
2015N242992_06	2018-AUG-29	Amendment No. 6
Changes were made to the protocol to update the study design to extend the Randomized Early Switch Phase through to 148 weeks instead of Week 52, delaying the late switch to Week 148 with long term follow-up through to completion of the study at Week 200.		

The rationale for this change is to collect and assess long-term comparative efficacy and safety data for DTG + 3TC FDC vs. a TAF-based regimen.

SPONSOR SIGNATORY:

PPD

PPD mberly YPPD
Vice Presid
Global Rese
ViiV Healthcare

8/29/18
Date

PPD

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

Role	Name	Daytime/Evening Phone Number/Email	Site Address
Primary Medical Monitor	PPD PPD MD	M: PPD PPD	ViiV Healthcare 980 Great West Road, Brentford, Middlesex, TW8 9GS, UK
Secondary Medical Monitor	PPD , MD	M: PPD PPD PPD	ViiV Healthcare 5 Moore Drive Research Triangle Park, NC 27709
Tertiary Medical Monitor	PPD MD	M: PPD PPD	ViiV Healthcare Mailstop UP4410 Collegeville, PA (USA)
SAE contact information	As above	As above	As above

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

US IND Sponsor Name and Legal Registered Address:
ViiV Healthcare
Five Moore Drive
P.O. 13398
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.

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

Regulatory Agency Identifying Number(s): US IND 127475/ EudraCT: 2015-004401-17

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 204862

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

TABLE OF CONTENTS

PAGE

1. PROTOCOL SYNOPSIS FOR STUDY 204862

Rationale

Study 204862 is being conducted to establish if human immunodeficiency virus type 1 (HIV-1) infected adult subjects with current virologic suppression on a ≥3-drug tenofovir alafenamide (TAF) based regimen (TBR) remain suppressed upon switching to a two-drug regimen of dolutegravir (DTG) 50 mg + lamivudine (3TC) 300 mg. This study also will provide important information regarding the safety of, and patient satisfaction with this two-drug regimen. This trial is designed to demonstrate the non-inferior antiviral activity of switching to DTG + 3TC once daily compared to continuation of TBR over 48 weeks. This study also will characterize the long-term antiviral activity, tolerability and safety of DTG + 3TC compared to TBR through Week 144 and characterize the long-term antiviral activity, tolerability and safety of DTG + 3TC through Week 200.

Objective(s)/Endpoint(s)

Objective	Endpoint
Primary	
To demonstrate the non-inferior antiviral activity of switching to DTG +3TC once daily compared to continuation of TBR over 48 weeks in HIV-1 infected, ART therapy (ART)-experienced, virologically suppressed subjects	Virologic failure endpoint as per FDA snapshot category at Week 48
Secondary	
To demonstrate the antiviral activity of switching to DTG +3TC once daily compared to continuation of TBR over 48 weeks	Proportion of subjects with plasma HIV-1 RNA <50 copies c/mL at Week 48 using the Snapshot algorithm for the ITT-E population
To demonstrate the antiviral activity of switching to DTG + 3TC once daily compared to continuation of TBR over 24 weeks, 96 weeks and 144 weeks	• Virologic failure endpoint as per FDA snapshot category at Weeks 24, 96 and 144 • Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Weeks 24, 96 and 144 using the Snapshot algorithm for the ITT-E population
To evaluate the immune effects of DTG + 3TC once daily compared to continuation of TBR over 24, 48, 96 and 144 weeks	• Change from Baseline in CD4+ cell count and in CD4+/CD8+ cell counts ratio at Weeks 24, 48, 96 and 144 • Incidence of disease progression (HIV-associated conditions, AIDS, and death) through Weeks 24, 48, 96, and 144
To evaluate the safety and tolerability of DTG + 3TC once daily compared to TBR over time	• Incidence and severity of AEs and laboratory abnormalities through 144 weeks • Proportion of subjects who discontinue treatment due to AEs through 144 weeks
To evaluate the effects of DTG + 3TC once daily on fasting lipids over time compared to TBR	Change from Baseline in fasting lipids at Weeks 24, 48, 96 and 144

Objective	Endpoint
To assess viral resistance in subjects meeting Virologic Withdrawal Criteria	Incidence of observed genotypic and phenotypic resistance to ARVs for subjects meeting Virologic Withdrawal Criteria
To evaluate renal (in urine and blood) and bone (in blood) biomarkers in subjects treated with DTG + 3TC compared to TBR	Change from Baseline in renal and bone biomarkers at Weeks 24, 48, 96 and 144
To assess health related quality of life for subjects treated with DTG + 3TC compared to TBR	Change from Baseline in health status using EQ-5D-5L at Weeks 24, 48, 96 and 144 (or Withdrawal from the study)

Overall Design

This is a 200-week, Phase III, randomized, open-label, active-controlled, multicenter, parallel-group study to assess the non-inferior antiviral activity and safety of replacing a TBR with a two-drug regimen of DTG + 3TC in HIV-infected adults who are virologically suppressed and stable on a TBR. The study will include a Screening Phase (up to 28 days), a Randomized Early Switch Phase (Day 1 up to Week 148), a Randomized Late Switch Phase (Week 148 up to Week 200), and a Continuation Phase (post Week 200) if DTG + 3TC fixed dose combination (FDC) is not yet approved and available locally. Approximately 550 HIV-1 infected adults who are on a stable TBR will be randomized 1:1 to switch to DTG + 3TC once daily (DTG + 3TC arm) for up to 200 weeks, or to continue their TBR for 148 weeks, at which time and if HIV-1 RNA <50 c/mL at Week 144 (or upon retest by Week 148), these subjects will switch to DTG + 3TC up to Week 200. For subjects randomized to the TBR, provisions will be in place, as needed and after discussion with the study team, to assist patients in obtaining their TBR during the study. For subjects who switch to DTG + 3TC at Week 148, a separate Late Switch Phase Time and Events Table is provided in Section 7.1.2 as these participants will be monitored closely for the first 24 weeks post-switch. Subjects who remain on DTG + 3TC will follow a separate Late Switch Phase Time and Events Table in Section 7.1.3.

The primary endpoint for the study is the proportion of participants who meet the Snapshot virologic failure criteria at Week 48 using the Intent-to-Treat Exposed (ITT-E) population. The Week 48 primary analysis will take place after the last subject has had their Week 48 viral load assessed, including any retests. Subjects randomized to DTG + 3TC will receive DTG + 3TC up to Week 200. Subjects randomized to TBR will have a Week 148 switch visit, allowing approximately 4 weeks for subjects who have a viral load ≥50 c/mL at Week 144 to have a retest prior to switch. The study will continue for at least 200 weeks.

The sample size is such that the study has 90% power to demonstrate non-inferiority using a 4% margin, assuming a true 2 % virologic failure rate at Week 48 and using a 2.5% one-sided alpha level.

A pharmacokinetic (PK) substudy in the DTG+3TC arm will be conducted to evaluate DTG and 3TC concentrations using a sparse PK sampling approach at designated visits

(See Section 11). In addition, intensive PK samples will be collected from a subgroup of subjects (approximately 30) enrolled at selected sites with the capability to perform intensive PK sampling.

An Independent Data Monitoring Committee (IDMC) will be instituted to ensure external objective medical and/or statistical review of efficacy and safety to protect the ethical interests and well-being of subjects and to protect the scientific validity of this study.

Treatment Arms and Duration

The study will include a Screening Phase (up to 28 days), a Randomized Early Switch Phase (Day 1 up to Week 148), a Randomized Late Switch Phase (Week 148 up to Week 200) and a Continuation Phase (post Week 200) if DTG + 3TC FDC is not yet approved and available locally. Subjects randomized to DTG + 3TC will receive DTG + 3TC up to Week 200. Subjects randomized to TBR will continue to take their current regimen up to Week 144, at which time and if HIV-1 RNA <50 c/mL at Week 144 (or upon retest by Week 148), these subjects will switch to DTG + 3TC up to Week 200. Randomization will be stratified by baseline third agent class (protease inhibitor [PI], integrase inhibitor [INI], or non-nucleoside reverse transcriptase inhibitor [NNRTI]).

The primary analysis at Week 48 will take place after the last subject completes up to 52 weeks on therapy, to allow for the collection of a confirmatory viral load measurement in subjects presenting with HIV-1 RNA ≥50 c/mL at the Week 48 visit. The secondary analysis at Week 24 will take place after the last subject completes up to 28 weeks on therapy, to allow for the collection of a confirmatory viral load measurement in subjects presenting with HIV-1 RNA ≥50 c/mL at the Week 24 visit. Further secondary analyses will take place at Week 96, 144 and 196.

All subjects who successfully complete 200 weeks of treatment will complete the study and transition to locally approved and available DTG + 3TC fixed-dose combination (FDC) and be managed as per standard of care at their study site. Prior to completion of the Week 200 visit, sites will need to have confirmation that DTG + 3TC FDC is locally available for study subjects. If DTG + 3TC FDC is not yet approved and available locally, ViiV Healthcare will continue to provide study drug in a Continuation Phase until:

- DTG + 3TC FDC is locally approved for use as a 2-drug regimen, and available to subjects (e.g., through public health services or through their usual health insurance payer), 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.

Assessments during the Continuation Phase are limited and will include plasma HIV-1 RNA and collection of AEs/SAEs.

No dose reductions, modifications, or changes in the frequency of any components of each regimen will be allowed during this study with the exception of a switch from a PI

boosted with ritonavir to the same PI boosted with cobicistat and vice versa. Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements is essential and required for study conduct.

Type and Number of Subjects

The target population to be enrolled is virologically suppressed subjects with HIV-1 infection on a stable TAF-based antiretroviral therapy (ART) with no evidence or history of drug resistance.

Assuming 30% screen failure rate, approximately 800 HIV-1-infected adult subjects will be screened to achieve 550 randomized subjects for a total of 275 evaluable subjects per treatment group. The study closed screening on 18 May 2018 with a total of 933 screened subjects and a total of 743 subjects were randomised.

Analysis

This study is designed to show that the antiviral effect of switching to a simplified two-drug regimen of DTG + 3TC once-daily is not inferior to continuation of TBR at week 48 in HIV-1 infected ART-experienced subjects.

Non-inferiority can be concluded if the upper bound of a two-sided 95% confidence interval for the difference in failure rates between the two treatment arms is smaller than 4%. If r_d is the virologic failure rate on DTG + 3TC and r_f is the virologic failure rate on the current ART regimen, then the hypotheses can be written as follows:

$$H_0: r_d - r_f \geq 4\% \qquad H_1: r_d - r_f < 4\%$$

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 virologic failure at Week 48 will be a Cochran-Mantel Haenszel test stratified by baseline third agent class (PI, INI, or NNRTI). A non-inferiority margin of 4% will be used for this comparison, where if the upper bound of the 95% confidence interval (CI) of the difference in failure rate between the 2 study arms is not more than 4%, non-inferiority will be demonstrated.

2. INTRODUCTION

Current human immunodeficiency virus (HIV) treatment guidelines recommend antiretroviral treatment (ART) 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, 2016; DHHS, 2016; EACS, 2015; IAS-USA, 2016]. These regimens are highly efficacious and generally well tolerated. However, since these regimens will need to be taken life-long, there is growing concern about their long-term toxicities and cost. As the potential for toxicities and cost are directly related to the number of antiretrovirals (ARVs) used, there is great interest from patients and clinicians in regimens that minimize the number of ARVs without sacrificing long-term antiviral efficacy.

Dolutegravir (DTG) is a potent dual cation binding INSTI, exhibiting rapid and potent (2.5 $\log_{10}$) reduction in viral load and a high barrier to resistance. In addition, DTG lacks many of the frequent drug interactions associated with other medications commonly taken by HIV-positive patients. The efficacy, pharmacokinetic (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]. DTG's efficacy and high barrier to resistance has been demonstrated in several DTG-based trials [Raffi, 2013; Walmsley, 2013; Clotet, 2014].

Lamivudine (3TC) is a potent cytidine nucleoside analogue with a favorable long-term safety profile. Available since 1995 as a single agent (EPIVIR), it is also available as part of three backbone fixed-dose combination (FDC) products (COMBIVIR, EPZICOM/KIVEXA and TRIUMEQ). Although 3TC monotherapy quickly selects for resistance due to a single point mutation at position M184V, 3TC retains residual antiviral activity against such mutants and helps prevent the emergence of resistance to other NRTI's [Eron, 1995; Kuritzkes, 1996].

A single tablet regimen (STR) of two potent, well-characterized and well-tolerated ARVs, DTG plus 3TC, may provide a novel 2-drug regimen that provides effective long-term antiviral suppression while limiting the risk of adverse reactions associated with ARV's. The combination of 3TC with DTG, with its high barrier to resistance, and ability to confer a rapid decline in HIV-1 ribonucleic acid (RNA), may be less likely to select for resistance. The expected efficacy and safety of a dual STR of DTG plus 3TC will make it suitable for both treatment-naïve individuals, and as a replacement treatment for ≥3-drug ART in virologically suppressed ("switch") patients.

2.1. Study Rationale

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 immunodeficiency syndrome (AIDS)-defining events (NADEs) such as cardiovascular disease, liver disease and cancer. These NADES are now the leading causes of morbidity and mortality among treated HIV-infected persons. The aetiologies of these NADEs 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. Compared to tenofovir disoproxil fumarate (TDF)-based regimens, tenofovir alafenamide (TAF) based regimens (TBRs) are associated with short-term improvements in renal and bone biomarkers in both treatment-naive and treatment-experienced persons [Genvoya, 2016]. However, the use of TAF leads to much higher intracellular tenofovir diphosphate (DP) levels compared to TDF, and the consequences of the long-term exposure to high intracellular tenofovir levels are unknown. 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]. It is of note that current TAF-regimens deliver four fold higher intracellular levels of tenofovir-DP (the active entity for both HIV-RT and human telomerase) than TDF-regimens and thus pose a greater concern for its effects on telomerase and normal cell proliferation. In addition, many of the current TAF-based single tablet regimens incorporate a boosting agent, cobicistat, while PI-containing regimens require boosting with ritonavir. With the increasing incidence of aging-related co-morbidities that comes with longer lifespan, drug-drug interactions from polypharmacy are an increasingly important issue. The use of cobicistat- and ritonavir-containing regimens may increase the risk of potentially harmful drug-drug interactions, and hence the need for optimized regimens involving drugs with minimal potential for such interactions.

Finally, if a 2-drug ART regimen is shown to be as effective and safe as conventional 3-drug regimens, the lower cost associated with taking one less drug for the lifetime of an HIV-infected person will have substantial individual and societal individual benefits.

One of the potential risks of a 2-drug regimen is the increase in virologic failure associated with the emergence of drug resistance. DTG, with its higher barrier to resistance, may reduce the risk of treatment-emergent resistance in patients taking a 2-drug regimen. The pivotal Phase 3 studies of DTG in naïve subjects have shown the absence of treatment-emergent INI or NRTI resistance mutations through 144+ weeks of treatment [Walmsley, 2013]. The absence of treatment emergent mutations to DTG or background agents in ART-naïve individuals, the potency of both DTG and 3TC, and the

well-tolerated safety profile of both drugs provides a strong rationale for the development of the DTG + 3TC STR as an important treatment option for patients.

The overall objective of the DTG + 3TC clinical development program is to develop a single tablet, fixed-dose, two-drug combination therapy regimen that is as effective as 3-drug ART in treating HIV-1 infection, is safe and well tolerated in the long-term, and has a high barrier to the emergence of viral resistance. A DTG + 3TC two-drug strategy may be effective in maintaining virologic suppression among treatment experienced subjects, while improving long-term safety and tolerability, and preserving future HIV-1 treatment options.

Study 204862 is being conducted to establish if human immunodeficiency virus type 1 (HIV-1) infected adult subjects with current virologic suppression on a TBR remain suppressed upon switching to a two-drug regimen with DTG + 3TC. This trial is designed to demonstrate the non-inferior antiviral activity of switching to DTG + 3TC once daily compared to continuation of a TBR over 48 weeks. To better understand the long-term differences in antiviral efficacy, safety and tolerability between DTG + 3TC and TAF-based regimens, the comparative phase of the study will be extended to 148 weeks. The originally planned Week 52 Switch Visit in the TBR arm will be moved to Week 148 to allow for 2 additional years of comparative follow-up. This study will also characterize the long-term antiviral activity, tolerability and safety of DTG + 3TC through Week 200.

2.2. Brief Background

By limiting the number of ARV's to which a patient is chronically exposed, 2-drug therapy has the potential benefit of preserving future treatment options, minimizing potential long term toxicity and decreasing the likelihood of drug-drug interactions (DDIs). Several studies have assessed the tolerability and durability of the virological response of a 2-drug ARV regimen as replacement for a ≥3-drug ARV regimen in individuals who were previously undetected on triple drug therapy. One such study was the OLE study which was an open label study in virologically suppressed HIV-1 infected individuals (HIV-1 RNA < 50 copies/mL) receiving a lopinavir (LPV)/r plus 3TC or emtricitabine (FTC) containing 3-drug regimen who were randomized to continue their current triple based regimen or have their therapy simplified to a dual regimen of LPV/r + 3TC [Arribas, 2015]. The primary endpoint was the proportion of patients free of therapeutic failure at 48 weeks. In a modified Intent to Treat (m-ITT) analysis, dual therapy with LPV/r + 3TC demonstrated non-inferior efficacy and comparable safety to LPV/r + 2 NRTIs, as maintenance therapy in virologically suppressed patients (91.5% vs. 90.9% respectively; 95% Confidence Interval (CI): -0.6% to 8.1%).

The SALT study [Perez-Molina, 2015] was a 96-week multicenter, randomized, open-label, clinical trial that compared atazanavir (ATV/r + 3TC with ATV/r + 2NRTIs (selected at the discretion of the investigator) in HIV-infected patients on a stable 3-drug regimen who switch therapy because of toxicity, intolerance, or simplification. The primary endpoint was to evaluate the non-inferior efficacy of maintenance therapy with ATV/r + 3TC compared to ATV/r + 2 NRTIs at 48 weeks (noninferiority margin, –12%) using the time to loss of virologic response (TLOVR) algorithm. At 48 weeks, 78.4% of

patients receiving triple therapy vs. 83.6% of patients switched to dual therapy had maintained HIV-RNA levels < 50 copies/mL thus establishing non-inferiority between these two treatment arms (difference between the arms 5.2; -4.8 to 15.2).
More recently, an INI-containing oral 2-drug regimen, cabotegravir (CAB) + rilpivirine (RPV), was evaluated as a maintenance therapy in HIV-infected persons who had virologic suppression after 24 weeks of 3-drug ART [Margolis, 2015]. The CAB + RPV arms showed comparative antiviral efficacy as the EFV + 2 NRTIs arm. Following 72 weeks of two-drug maintenance therapy (Week 96), in the ITT maintenance = exposed population, 86% of CAB + RPV subjects and 83% of EFV + 2 NRTIs subjects remained virologically suppressed. Virologic failure was seen in 4% of the CAB arms and 2% of the EFV+2 NRTI arm.

GEMINI-1 and GEMINI-2 are two identical global, double-blind, multicentre Phase III studies evaluating the efficacy and safety of DTG + 3TC once daily in treatment-naïve HIV-1-infected adults with Screening HIV-1 ≤500,000 c/mL. At 48 weeks, dual therapy with DTG + 3TC demonstrated non-inferior efficacy to DTG + TDF/FTC (in the primary endpoint: proportion of subjects with plasma HIV-1 RNA<50 c/ml by FDA Snapshot in the pooled ITT-E population [DTG/3TC n=716; DTG/TDF/FTC n= 717] 91% vs. 93% respectively, adjusted difference (95% CI) -1.7 (-4.4, 1.1). Across both studies, 6 participants on DTG + 3TC and 4 participants on DTG + TDF/FTC met protocol-defined virologic withdrawal criteria and none had treatment-emergent INSTI or NRTI resistance mutations. Overall, the rates of AEs were similar between arms, with low rates of withdrawals due to AEs for both arms [Cahn, 2018].

TAF, a HIV-1 nucleotide analogue reverse transcriptase inhibitor (NRTI), is a novel targeted prodrug of tenofovir that has demonstrated antiviral efficacy similar to and at much lower dose than that of TDF. TAF has also shown improvement in surrogate laboratory markers of renal and bone safety as compared to TDF in clinical trials in combination with other antiretroviral drugs. Combinations of TAF-containing regimens including rilpivirine/FTC/TAF (Odefsey), elvitegravir (EVG)/cobicistat/FTC/TAF (Genvoya) and FTC/TAF (Descovy) + a 3rd agent (INI, NNRTI or boosted PI) are indicated for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older who have no ART history or to replace the current ARV regimen in those who are virologically-suppressed (HIV-1 RNA<50 copies/mL) on a stable ARV regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance [Odefsey, 2016; Genvoya, 2016; Descovy, 2016].

3. OBJECTIVE(S) AND ENDPOINT(S)

Objective	Endpoint
Primary	
To demonstrate the non-inferior antiviral activity of switching to DTG +3TC once daily compared to continuation of TBR over 48 weeks in HIV-1 infected, ART therapy (ART)-experienced, virologically suppressed subjects	Virologic failure endpoint as per FDA snapshot category at Week 48
Secondary	
To demonstrate the antiviral activity of switching to DTG + 3TC once daily compared to continuation of TBR over 48 weeks	Proportion of subjects with plasma HIV-1 RNA <50 copies c/mL at Week 48 using the Snapshot algorithm for the ITT-E population
To demonstrate the antiviral activity of switching to DTG + 3TC once daily compared to continuation of TBR over 24, 96 and 144 weeks	• Virologic failure endpoint as per FDA snapshot category at Weeks 24, 96 and 144 • Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Weeks 24, 96 and 144 using the Snapshot algorithm for the ITT-E population
To evaluate the immune effects of DTG + 3TC once daily compared to continuation of TBR over 24, 48, 96 and 144 weeks	• Change from Baseline in CD4+ cell count and in CD4+/CD8+ cell count ratio at Weeks 24, 48, 96 and 144 • Incidence of disease progression (HIV-associated conditions, AIDS, and death) through Weeks 24, 48, 96 and 144
To evaluate the safety and tolerability of DTG + 3TC once daily compared to TBR over time	• Incidence and severity of AEs and laboratory abnormalities through 144 weeks • Proportion of subjects who discontinue treatment due to AEs through 144 weeks
To evaluate the effects of DTG + 3TC once daily on fasting lipids over time compared to TBR	Change from Baseline in fasting lipids at Weeks 24, 48, 96 and 144
To assess viral resistance in subjects meeting Virologic Withdrawal Criteria	Incidence of observed genotypic and phenotypic resistance to ARVs for subjects meeting Virologic Withdrawal Criteria
To evaluate renal (in urine and blood) and bone (in blood) biomarkers in subjects treated with DTG + 3TC compared to TBR	Change from Baseline in renal and bone biomarkers at Weeks 24, 48, 96 and 144
To assess health related quality of life for subjects treated with DTG + 3TC compared to TBR	Change from Baseline in health status using EQ-5D-5L at Weeks 24, 48, 96 and 144 (or Withdrawal from the study)

Objective	Endpoint
Exploratory	
To evaluate the effect of patient characteristics (e.g., demographic factors, Baseline CD4) on antiviral and immunological responses to DTG + 3TC compared to TBR	• Proportion of subjects by subgroup(s) (e.g., by age, gender, Baseline CD4) with plasma HIV-1 RNA <50 c/mL using the Snapshot algorithm at Weeks 24, 48, 96 and 144 • Change from Baseline in CD4+ cell counts at Weeks 24, 48, 96 and 144 by patient subgroups
To assess willingness to switch for subjects treated with DTG + 3TC compared to TBR	Reasons for Willingness to Switch at Day 1
To evaluate biomarkers of telomerase function in a subset of subjects treated with DTG + 3TC compared to TBR.	Change from baseline in biomarkers of telomerase function at Weeks 48, 96 and 144
To evaluate inflammation biomarkers and insulin resistance in a subset of subjects treated with DTG+ 3TC compared to TBR	Change from Baseline in inflammation biomarkers and homeostasis model of assessment-insulin resistance (HOMA-IR) at Weeks 48, 96 and 144
To evaluate the longer term antiviral and immunological effects, safety and tolerability of DTG + 3TC once daily in subjects treated with DTG + 3TC since the Early Switch Phase	For subjects in the DTG + 3TC arm since Early Switch Phase: • Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 196 using the Snapshot algorithm for the ITT-E population • Change from Baseline in CD4+ lymphocyte count and in CD4+/CD8+ cell count ratio at Week 196 • Incidence and severity of AEs and laboratory abnormalities over 196 weeks • Proportion of subjects who discontinue treatment due to AEs over 196 weeks • Incidence of disease progression (HIV associated conditions, AIDS and death) through Week 196 • Change from Baseline in renal and bone biomarkers at Week 196 • Change from baseline in biomarkers of inflammation, HOMA-IR and telomerase function at week 196
To evaluate the antiviral and immunological effects, safety and tolerability of DTG + 3TC for subjects switching in the Late Switch Phase	For subjects switching to DTG + 3TC in the Late Switch Phase: • Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 196 using the Snapshot algorithm for the ITT-E population • Change from Baseline in CD4+ lymphocyte count and in CD4+/CD8+ cell count ratio at Week 196

Objective	Endpoint
	• Incidence and severity of AEs and laboratory abnormalities during the Late Switch Phase • Proportion of subjects who discontinue treatment due to AEs during the Late Switch Phase • Incidence of disease progression (HIV associated conditions, AIDS and death) during the Late Switch Phase • Change from Baseline in renal and bone biomarkers at Week 196 • Change from baseline in biomarkers of inflammation, HOMA-IR and telomerase function at week 196
To assess the steady-state DTG and 3TC exposure in HIV-1 infected patients	Steady state plasma PK parameters of DTG and 3TC will be assessed using intensive PK collected at week 4.
To characterize the DTG and 3TC steady-state PK of the DTG/3TC FDC in HIV-1 infected patients	Population estimates of DTG and 3TC PK parameters (e.g. apparent clearance [CL/F], apparent volume of distribution [V/F]) using DTG and 3TC intensive and sparse plasma concentrations at Weeks, 4, 8, 12, 24, 36 and 48

4. STUDY DESIGN

4.1. Overall Design

This is a 200-week, Phase III, randomized, open-label, active-controlled, multicenter, parallel-group study to assess the non-inferior antiviral activity and safety of replacing a TBR with a two-drug regimen of DTG + 3TC in HIV-infected adults who are virologically suppressed and stable on a TBR. The study will include a Screening Phase (up to 28 days), an Early Switch Phase (Day 1 up to Week 148) a Late Switch Phase (Week 148 up to Week 200), and a Continuation Phase (post Week 200) if DTG + 3TC FDC is not yet approved and available locally. Approximately 550 HIV-1 infected adults who are on a stable TBR will be randomized 1:1 to switch to DTG + 3TC once daily (DTG + 3TC arm) for up to 200 weeks, or to continue their TBR for 148 weeks, at which time and if HIV-1 RNA <50 c/mL at Week 144 (or upon retest by Week 148), these subjects will switch to DTG + 3TC up to Week 200. For subjects randomized to the TBR, provisions will be in place, as needed and after discussion with the study team, to assist patients in obtaining their TBR during the study. For subjects who switch to DTG + 3TC at Week 148, a separate Late Switch Phase Time and Events Table is provided in Section 7.1.2 as these participants will be monitored closely for the first 24 weeks post-switch. Subjects who remain on DTG + 3TC will follow a separate Late Switch Phase Time and Events Table in Section 7.1.3.

The primary endpoint for the study is the proportion of participants who meet the Snapshot virologic failure criteria at Week 48 using the Intent-to-Treat Exposed (ITT-E) population. The Week 48 primary analysis will take place after the last subject has had their Week 48 viral load assessed, including any retests. Subjects randomized to DTG + 3TC will receive DTG + 3TC up to Week 200. Subjects randomized to TBR will have a Week 148 switch visit, allowing approximately 4 weeks for subjects who have a viral load ≥50 c/mL at Week 144 to have a retest prior to switch. The study will continue for at least 200 weeks.

All subjects who successfully complete 200 weeks of treatment will complete the study and transition to locally approved and available DTG + 3TC fixed-dose combination (FDC) and be managed as per standard of care at their study site. Prior to completion of the Week 200 visit, sites will need to have confirmation that DTG + 3TC FDC is locally available for study subjects. If DTG + 3TC FDC is not yet approved and available locally, ViiV Healthcare will continue to provide study drug in a Continuation Phase as outlined in Section 4.2.4.

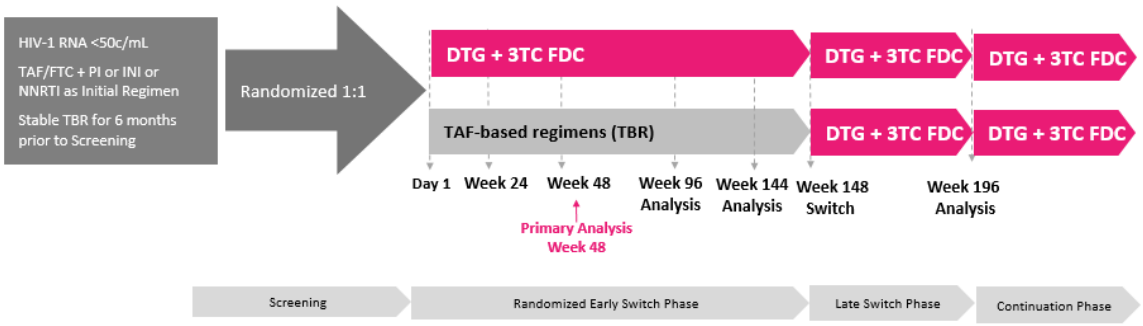
No dose reductions, modifications, or changes in the frequency of any components of each regimen will be allowed during this study with the exception of a switch from a PI boosted with ritonavir to the same PI boosted with cobicistat and vice versa. Protocol waivers or exemptions are not allowed. Adherence to the study design requirements, including those specified in the Time and Events Table (Section 7.1), are essential and required for study conduct. If deviations are required for the management of immediate safety concerns, these should be communicated promptly to the study medical monitor.

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 the study. An ad-hoc review of data by the IDMC will be triggered whenever the number of confirmed virologic withdrawals (CVWs) exceeds thresholds pre-specified in the IDMC charter. Full details of the methods, timing, decision criteria and operating characteristics will be pre-specified in the IDMC Charter. Communication received from the IDMC regarding the status of the study will be shared with investigators in a timely manner.

A pharmacokinetic (PK) substudy in the DTG+3TC arm will be conducted to evaluate DTG and 3TC concentrations using a sparse PK sampling approach at designated visits (See Section 11). In addition, intensive PK samples will be collected from a subgroup of subjects (approximately 30) enrolled at selected sites with the capability to perform intensive PK sampling.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Reference Manual (SRM), which is available on the online Study Web Portal. The SRM will provide site personnel with administrative and detailed technical information.

Figure 1 Study Schematic



4.2. Treatment Arms and Duration

4.2.1. Screening Period (Up to 28 days)

Randomization may occur as soon as all screening procedures and entry criteria data are confirmed and **available on file** at the site. The Screening of up to 28 days is to allow receipt of all screening assessment results, to enable source document verification of entry criteria and to accommodate scheduling.

4.2.2. Early Switch Phase (Day 1 up to Week 148)

Subjects who fulfil all eligibility requirements will be randomly assigned 1:1 to receive DTG + 3TC FDC once daily up to Week 200, or continue their TBR up to Week 148. The DTG + 3TC and TBR will be administered in an open-label fashion throughout the study. For subjects randomized to the TBR, provisions will be in place, as needed and

after discussion with the study team, to assist patients in obtaining their TBR during the study.

Following the Week 144 visit, subjects will stay on DTG + 3TC or their TBR for another 4 weeks so that the result from the Week 144 HIV-1 RNA testing is known. All subjects with a viral load ≥50 c/mL must have plasma HIV-1 RNA levels re-assessed within approximately 2-4 weeks. This will allow any subject in the TBR arm with a viral load ≥50 c/mL at Week 144 to have their viral load confirmed by a second measurement performed within approximately 2-4 weeks while still on their TBR regimen.

The primary analysis will take place after the last subject completes up to 52 weeks on therapy, to allow for the collection of a confirmatory viral load measurement in subjects presenting with HIV-1 RNA ≥50 c/mL at the Week 48 visit. If the retest HIV-1 RNA is <50 c/mL, then the subject will be considered to have met the criteria for virologic responder by Food Drugs and Administration (FDA)'s Snapshot algorithm at Week 48. If the retest HIV-1 RNA is ≥50 c/mL, then the subject will be considered to be a virologic non-responder at Week 48 by Snapshot.

The secondary analysis at Week 24 will take place after the last subject completes up to 28 weeks on therapy, as needed, to allow for the collection of a confirmatory viral load measurement in subjects presenting with HIV-1 RNA ≥50 c/mL at Week 24.

The secondary analysis at Week 96 will take place after the last subject completes up to 100 weeks on therapy, as needed, to allow for the collection of a confirmatory viral load measurement in subjects presenting with HIV-1 RNA ≥50 c/mL at Week 96.

The secondary analysis at Week 144 will take place after the last subject completes up to 148 weeks on therapy, as needed, to allow for the collection of a confirmatory viral load measurement prior to Week 148 switch visit in subjects presenting with HIV-1 RNA ≥50 c/mL at Week 144. If the retest HIV-1 RNA is <50 c/mL, subjects in the TBR arm will be considered eligible to switch to DTG + 3TC at Week 148. If the retest HIV-1 RNA is ≥50 c/mL, the subjects in the TBR arm will be considered ineligible to switch to DTG + 3TC. Subjects who are ineligible to switch will be withdrawn from the study. Thus, the treatment extension up to Week 148 will allow for as complete an assessment as possible of treatment response in the analysis at Week 144 within the Snapshot window.

4.2.3. Late Switch Phase (Week 148 to Week 200)

At Week 144, subjects randomly assigned to DTG + 3TC and with HIV-1 RNA <50 c/mL will continue on that treatment through Week 200. At Week 148, subjects randomly assigned to continue their TBR and with HIV-1 RNA <50 c/mL at Week 144 (or upon retest) will switch to DTG + 3TC once daily and be followed up to Week 200. For subjects who switch to DTG + 3TC at Week 148, a separate Late Switch Phase Time and Events Table is provided in Section 7.1.2 as these participants will be monitored closely for the first 24 weeks post-switch. Subjects who remain on DTG + 3TC will follow a separate Late Switch Phase Time and Events Table in Section 7.1.3.

The analysis at Week 196 will take place after the last subject completes 200 weeks on therapy, as needed, to allow for the collection of a confirmatory viral load measurement in subjects presenting with HIV-1 RNA ≥50 c/mL at Week 196.

4.2.4. Continuation Phase (Post Week 200)

At the end of the study at Week 200, subjects will transition to locally approved and available DTG + 3TC FDC and be managed as per standard of care at their study site. Prior to completion of the Week 200 visit, sites will need to have confirmation that DTG + 3TC FDC is locally available for study subjects. If DTG + 3TC FDC is not yet approved and available locally, ViiV Healthcare will continue to provide study drug in a Continuation Phase until:

- DTG + 3TC FDC is locally approved for use as a 2-drug regimen, and available to subjects (e.g., through public health services or through their usual health insurance payer), 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.

Assessments during the Continuation Phase are limited and will include plasma HIV-1 RNA and collection of AEs/SAEs.

4.3. Type and Number of Subjects

The target population to be enrolled is HIV-1 infected adults who are virologically suppressed on a TBR (As a first-line regimen with specific allowed switches as defined in inclusion criterion 5) and with no evidence or history of ARV drug-resistance.

Assuming 30% screen failure rate, approximately 800 HIV-1-infected adult subjects will be screened to achieve 550 randomized subjects for a total of 275 evaluable subjects per treatment group. The study closed screening on 18 May 2018 with a total of 933 screened subjects and a total of 743 subjects were randomized.

4.4. Design Justification

The design of this study (1:1 randomized, open-label, active-controlled, multicenter, parallel group, non-inferiority study) is well established for confirming the non-inferiority of an investigational agent compared with an active ART standard-of-care regimen and generally is accepted by regulatory authorities as rigorous proof of antiviral activity. The primary endpoint, proportion of subjects defined as virologic failures by the FDA Snapshot algorithm, is recommended in the FDA's 2015 guidance document for assessing efficacy in Switch Trials [CDER, 2015]. The key secondary endpoint, proportion of subjects at Week 48 with plasma HIV-1 RNA<50 c/mL, is also a well-established surrogate endpoint for prognosis of HIV-1 infection and disease progression [CDER, 2015].

Several studies have demonstrated the value/feasibility of a switch study design, an approach that has been shown to generate valuable data supporting ARV combinations that allow dosing flexibility, reduced toxicity and/or drug interactions or a reduction in pill burden. A simplified ARV regimen may also contribute to increased medication adherence and reduced HIV transmission. A potential disadvantage of a switch study design is that effective, well-tolerated ART is discontinued at the time of switching to the simplified regimen [Carr, 2012].

Previous studies have shown the non-inferiority of a 2-drug regimen in maintaining virologic suppression when HIV-infected persons who were virologically suppressed on a 3-drug regimen were switched to a 2-drug regimen. In OLE, switching to a 2-drug regimen of LPV/r + 3TC/FTC was non-inferior to continuing a 3-drug regimen of LPV/r + 2 NRTIs in HIV-infected persons who were virologically stable on LPV/r + 2 NRTIs [Arribas, 2015]. Protocol-defined virologic failure was 2.7% in either arm. In SALT, ATV/r + 3TC was non-inferior to a ATV/r + 2 NRTIs in maintaining virologic suppression in HIV-infected patients who switched ART for reasons of toxicity, intolerance or simplification; virologic failure was seen in 4% and 3% of the 2- and 3-drug arms, respectively [Perez-Molina, 2015]. More recently, an INI-containing oral 2-drug regimen, cabotegravir (CAB) + rilpivirine (RPV), was evaluated as a maintenance therapy in HIV-infected persons who had virologic suppression after 24 weeks of 3-drug ART [Margolis, 2015]. The CAB + RPV arms showed comparative antiviral efficacy as the EFV + 2 NRTIs arm. Following 72 weeks of two-drug maintenance therapy (Week 96), in the ITT maintenance = exposed population, 86% of CAB + RPV subjects and 83% of EFV + 2 NRTIs subjects remained virologically suppressed. Virologic failure was seen in 4% of the CAB arms and 2% of the EFV+2 NRTI arm.

TAF-based regimens including rilpivirine/FTC/TAF, EVG/cobicistat/FTC/TAF, and FTC/TAF + either INI, NNRTI or boosted PI are indicated for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older who have no ART history or to replace the current ARV regimen in those who are virologically-suppressed (HIV-1 RNA<50 copies/mL) on a stable ARV regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance [Odefsey, 2016; Genvoya, 2016; Descovy, 2016]. Switching to EVG/cobicistat/FTC/TAF from one containing either TDF/FTC/EFV, TDF/FTC/ATV/r, TDF/FTC/ATV/cobicistat or TDF/FTC/EVG/cobicistat was non-inferior for maintenance of viral suppression and led to improvements in surrogate markers of bone and renal function [Mills, 2016]. Similarly, switching the background regimen from TDF/FTC to TAF/FTC was non-inferior in maintaining virological suppression [Gallant, 2016]. TBR's are not recommended in patients with estimated creatinine clearance below 30 mL/min, or in patients with severe hepatic impairment.

In this study, subjects will be randomized 1:1 to switch to DTG + 3TC from a TBR at Day 1 or stay on their TBR for up to 148 weeks. The primary endpoint will be evaluated at Week 48 using a 4% non-inferiority (NI) margin. This study is evaluating the rate of Snapshot algorithm measured virological failure in already suppressed subjects to test the hypothesis that maintenance of the suppression of HIV-1 replication by DTG + 3TC will be non-inferior to that observed in the TBR arm of the study through Week 48. To assess

the durability of HIV-1 RNA suppression by DTG + 3TC, subjects will remain on DTG + 3TC through Week 200.

After Week 96, study visits will be extended to every 6 months (instead of 12 weekly visits) except in countries where visits are required every 3 months per standard of care. For subjects who switch to DTG + 3TC at Week 148, a separate Late Switch Phase Time and Events Table is provided in Section 7.1.2 as these participants will be monitored closely for the first 24 weeks post-switch. Subjects who remain on DTG + 3TC will follow a separate Late Switch Phase Time and Events Table in Section 7.1.3. This amended design will allow a longer period of comparison of antiviral efficacy, safety and tolerability between DTG + 3TC and TAF-based regimens. Long-term comparison of outcomes between regimens is important in a disease where treatment is provided life-long.

The open-label design best suits the objectives of this study. A double-dummy design could not be undertaken given the increase in pill burden that would result from blinding, the differing requirements for dosing a variety of TBRs with food, and wide variety of potential drug-drug interactions. An increase in pill burden could hinder compliance substantially and discourage subject enrolment. The use of the FDA snapshot algorithm for assessing the proportion of subjects with virologic failure as an objective primary endpoint will help reduce biases inherent to an open label study design.

4.5. Dose Justification

To date, the efficacy, PK, safety, and drug interaction potential of DTG and 3TC as individual agents have been evaluated in two extensive clinical development programs of Phase I to III clinical trials. As individual agents, DTG and 3TC are both approved and marketed as TIVICAY 50 mg once daily and Epivir 300 mg once daily, respectively. These doses will be used in the current study.

Comprehensive clinical studies have been conducted with the individual DTG and 3TC products, including clinical pharmacology studies evaluating potential drug-drug interactions between each of these active ingredients and other agents. There are no known clinically relevant PK interactions between DTG and 3TC with concomitant dosing.

A summary of the overall clinical development for both products is available in the IBs and or Product Insert(s) for the respective products (refer to the most current version of product inserts and of the IB and any IB supplements [GSK Document Number RM2007/00683/11, GSK Document Number 2017N352880_00, GSK Document Number 2017N352880_01]; Dolutegravir Product Insert, 2017; Epivir Product Insert, 2017).

A double-dummy design could not be undertaken given the increase in pill burden that would result from blinding, and the variable dosing requirements with food for each unique TBR.

Based on the preliminary results of the pivotal bioequivalence study (204994), a bilayer tablet formulation with a core which utilizes the same formulation in the respective layers as the single entity tablets was selected. When administered in the fasted state, the

bilayer tablet demonstrated bioequivalence to the single entity tablets for dolutegravir area under the curve zero to infinity (AUC(0-∞)) & maximum concentration (Cmax) and lamivudine AUC(0-∞). However, the bilayer tablet showed a modest increase in lamivudine Cmax compared to the single entity tablet, which is not considered to be clinically significant. PK of the FDC components will be evaluated using a combination of intensive and sparse sampling.

4.6. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with DTG or 3TC can be found in the IBs and product labels.

The following section outlines the risk assessment and mitigation strategy for DTG and 3TC in this protocol. Where available, the approved country product label should be referenced. For the TBRs regimen, the approved country product labels for the respective drugs should be referenced.

4.6.1. Risk Assessment

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

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy[a]
Investigational Product (IP) [DTG and 3TC] Refer to IBs for additional information		
DTG: Hypersensitivity reaction (HSR) and rash	**DTG:** 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. Specific/detailed toxicity management guidance is provided for rash (Section 13.2.1.6). The subject informed consent form (ICF) includes information on this risk and the actions subjects should take in the event of a HSR or associated signs and symptoms
DTG: Drug induced liver injury (DILI) and other clinically significant liver chemistry elevations **3TC**: Use in HBV co-infected patients and emergence of HBV variants resistant to 3TC	**DTG:** Non-clinical data suggested a possible, albeit low, risk for hepatobiliary toxicity with DTG. Drug-related hepatitis is considered an uncommon risk for ART containing DTG regardless of dose or treatment population. For 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. **3TC**: 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 HBV variants associated with resistance to 3TC has been reported in HIV-1-	Subjects meeting any of the following criteria during the screening period are excluded from participating. • Alanine aminotransferase (ALT) ≥5 times the upper limit of normal (ULN) or ALT ≥3xULN and bilirubin ≥1.5x ULN (with >35% direct bilirubin) • Subjects positive for Hepatitis B surface antigen (+HBsAg) • Subjects negative for HBsAg and anti-HBsAg and positive for anti-HBc and HBV DNA. • Anticipated need for any hepatitis C virus (HCV) therapy during the first 48 weeks of the study, and for HCV therapy based on interferon or for any drugs that have a potential for adverse drug-drug interactions with study treatment throughout the entire study period. Specific/detailed liver stopping criteria and toxicity management

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy[a]
Investigational Product (IP) [DTG and 3TC] Refer to IBs for additional information		
	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.	guidance is provided for suspected DILI or other clinically significant liver chemistry elevations (Section 13.2).
DTG: Psychiatric disorders	**DTG:** Psychiatric disorders including suicidal ideation and behaviors are common in HIV-infected patients. Events of suicidal ideation, attempt, behaviour and completion were observed in clinical studies of DTG, primarily in subjects with a pre-existing history of depression or other psychiatric illness. The psychiatric profile for DTG (including suicidality, depression, bipolar and hypomania, anxiety and abnormal dreams) was similar to RAL- or favorable compared with EFV- based regimens. The reporting rate for insomnia was statistically higher for blinded DTG+ abacavir/lamivudine (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. Because of the elevated risk in the HIV- infected population, treatment emergent assessment of suicidality will be monitored during this study through the end of the continuation phase. Investigators are advised to consider mental health consultation or referral for subjects who experience signs of suicidal ideation or behaviour (See Section 7.4.7). The subject informed consent form includes information on the risk of depression and suicidal ideation and behavior.
DTG: Increased rates of virologic failure/ Observed Resistance	Virologically suppressed subjects switching from stable ART to DTG + 3TC may experience virologic failure/breakthrough and development of resistance. **DTG:** Week 96 and Week 144 analyses for the Phase III/IIIb clinical studies supported the efficacy findings from earlier analyses, and demonstrated robust maintenance of viral suppression with no finding of HIV-1 resistance in treatment-naïve subjects. **3TC**: M184V is the common single mutation that leads to full resistance to 3TC.	Subjects with any switch to a second line regimen due to previous virologic failure and subjects with evidence of pre-existing viral resistance mutation (including M184I/V) are excluded from this study. Genotypic resistance testing results must be reviewed by ViiV Virology to ensure subjects with exclusionary mutations are not randomized. Subjects will have HIV-1 RNA measured at routine study visits. An IDMC will be instituted to ensure external objective medical and/or statistical review of efficacy and safety.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy[a]
Investigational Product (IP) [DTG and 3TC] Refer to IBs for additional information		
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 (OCT-2), resulting in potentially life-threatening toxicity.	The co-administration of DTG with dofetilide or pilsicainide is prohibited in the study (Section 6.11.2.1).
DTG and 3TC: Renal function	**DTG**: Mild elevations of creatinine have been observed with DTG which are related to a likely benign effect on creatinine secretion with blockade of OCT-2. DTG has been shown to have no significant effect on glomerular filtration rate (GFR) or effective renal plasma flow. **3TC**: 3TC is eliminated by renal excretion and exposures increase in patients with renal dysfunction.	Specific/detailed toxicity management guidance is provided for subjects who develop a decline in renal function (Section 13.2.1.3). Creatinine clearance 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. Subjects with creatinine clearance <50 mL/min are excluded from participation in this study.
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 13.2.1.8).
DTG: Neural tube defects	In one ongoing birth outcome surveillance study in Botswana, early results from an unplanned interim analysis show that 4/426 (0.9%) of women who were taking DTG when they became pregnant had babies with neural tube defects compared to a background rate of 0.1%.	1. A female subject is eligible to participate if she is not pregnant, not lactating, and, if she is a female of reproductive potential, agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see Appendix 3, Section 13.3.1) from 30 days prior to the first dose of study medication and for at least 2 weeks after the last dose of study medication. 2. Women who are breastfeeding or plan to become pregnant or breastfeed during the study are excluded. 3. Women who become pregnant, or who desire to be pregnant while in the study, or who state they no longer are willing to

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy[a]
Investigational Product (IP) [DTG and 3TC] Refer to IBs for additional information		
		comply with the approved pregnancy avoidance methods, will have study treatment discontinued and will be withdrawn from the study. 4. Females of reproductive potential are reminded re: pregnancy avoidance and adherence to contraception requirements at every study visit. 5. Pregnancy status is monitored at every study visit and using home-based urine pregnancy tests at approximately 12 week intervals when study visits are extended to every 24 weeks.

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)/ViiV 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

Individually, DTG and 3TC are 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 (including EFV and those requiring a PK booster). In addition, the high barrier to resistance observed with DTG should help protect against the development of resistance to both components of the DTG + 3TC regimen. Individually, DTG and 3TC in combination with other ARVs have demonstrated durable virologic and immunologic response.

In general, switching subjects to a DTG + 3TC regimen from a dual NRTI-based 3-drug regimen may increase tolerability, reduce the frequency of adverse events associated with NRTI-based regimens and/or drug-drug interactions. Study participants also may benefit from the medical tests and screening procedures performed as part of this study.

4.6.3. Overall Benefit:Risk Conclusion

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with DTG + 3TC are justified by the anticipated benefits that may be afforded to study subjects switching to this 2-drug regimen.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the ViiV investigational product or other study treatment that may impact subject eligibility is provided in the Product Insert(s) for DTG and for 3TC.

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

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 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. Aged 18 years or older (or older where required by local regulatory agencies), at the time of signing the informed consent.
TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. HIV-1 infected men or women. 3. Documented evidence of at least two plasma HIV-1 RNA measurements <50 c/mL in the 12 months prior to Screening: one within the 6 to 12 month window, and one within 6 months prior to Screening. 4. Plasma HIV-1 RNA <50 c/mL at Screening. 5. Must be on uninterrupted ART for at least 6 months prior to screening. Only the following regimens are allowed: a. Subjects on a TAF-based regimen for at least 6 months as the initial regimen, or b. Subjects who switched from a TDF first regimen to TAF, without any changes to the other drugs in their regimen, and have been on the TAF-based regimen for at

least 3 months immediately prior to Screening, i.e., the only switch made is from TDF to TAF. This switch must have occurred due to tolerability/safety, access to medications, or convenience/simplification, and must NOT have been done for suspected or established treatment failure. A switch from a PI boosted with RTV to the *same* PI boosted with cobicistat is allowed (and vice versa).

SEX

6. 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 screen and a negative urine hCG test at Randomization (a local serum hCG test at Randomization is allowed if it can be done, and results obtained, within 24 hours prior to randomization)], 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
   - Post-menopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels)]. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment.

b. ***Reproductive potential*** and agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see Section 13.3) from 30 days prior to the first dose of study medication and for at least 2 weeks after the last dose of study medication.

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

All subjects participating in the study should be counseled 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

7. 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. Eligible subjects or their legal guardians must sign a written Informed Consent Form before any protocol-specified assessments are conducted.

OTHER
8. Subjects enrolled in France must be 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. Historical or current CD4 cell counts less than 200 cells/mm^3 are NOT exclusionary. 3. Subjects with severe hepatic impairment (Class C) as determined by Child-Pugh classification (see Section 13.4). 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 Hepatitis B virus (HBV) infection based on the results of testing at Screening for Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody (anti-HBc), Hepatitis B surface antigen antibody (anti-HBs) 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. Anti-HBc must be either total anti-HBc or anti-HBc immunoglobulin G (IgG), and NOT anti-HBc IgM. 6. Anticipated need for any hepatitis C virus (HCV) therapy during the first 48 weeks of the study, or anticipated need for HCV therapy based on interferon or for 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 7 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. 10. Subjects who in the investigator's judgment, poses a significant suicidality 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 • radiation therapy • cytotoxic chemotherapeutic agents • any systemic immune suppressant 13. 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 IP. 14. Use of any regimen consisting of single or dual ART.
LABORATORY VALUES OR CLINICAL ASSESSMENTS AT SCREENING
15. Any evidence of major NRTI mutation or presence of any major INSTI resistance-associated mutation [Wensing, 2017] in any available prior resistance genotype assay test result, if known, ***must*** be provided to ViiV after screening and before randomization for review by ViiV Virology. Refer to the most recent version of IAS Guidelines, SRM, and Section 7.2.1 (Screening Assessments) for more information. 16. Any verified Grade 4 laboratory abnormality. 17. Alanine aminotransferase (ALT) ≥5 times the upper limit of normal (ULN) *or* ALT ≥3xULN and bilirubin ≥1.5xULN (with >35% direct bilirubin). 18. Creatinine clearance of <50 mL/min/1.73m^2 via CKD-EPI method.

EXCLUSIONARY CRITERIA PRIOR TO SCREENING OR DAY 1
19. Within the 6 to 12 month window prior to Screening and after confirmed suppression to <50 c/mL, any plasma HIV-1 RNA measurement >200 c/mL. 20. Within the 6 to 12 month window prior to Screening and after confirmed suppression to <50 c/mL, 2 or more plasma HIV-1 RNA measurements ≥50 c/mL. 21. Within 6 months prior to Screening and after confirmed suppression to <50 c/mL on current ART regimen, any plasma HIV-1 RNA measurement ≥50 c/mL. 22. Any drug holiday during the 6 months prior to Screening, except for brief periods (less than 1 month) where all ART was stopped due to tolerability and/or safety concerns. 23. Any history of switch to another regimen, defined as change of a single drug or multiple drugs simultaneously, due to virologic failure to therapy (defined as a confirmed plasma HIV-1 RNA ≥400 c/mL.
COUNTRY SPECIFIC REQUIREMENTS
24. Subjects enrolled in France (or in other countries as required by local regulations or Ethics Committee/Institutional Review Board [IRB]) who: • participated in any study using an investigational drug or vaccine 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
- participate simultaneously in another clinical study.

5.3. Screening Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. 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 any Serious Adverse Events (see Section 7.4.1.6).

Subjects are allowed to re-screen for this study one time (except where screen HIV-1 plasma RNA ≥50 c/mL or where exclusionary HIV-1 resistance was present). Re-screening will require a new subject number. A single repeat test (re-test) per analyte or assessment is allowed during the screening period to determine eligibility. However, a repeat HIV-1 RNA, if HIV-1 RNA was ≥50-c/mL is not allowed.

Laboratory results provided from central laboratory services will be used to assess eligibility. In exceptional circumstances only, if a central lab result cannot be generated, local labs can be reviewed and approved by the Medical Monitor, for consideration of participant eligibility, except for plasma HIV-1 RNA.

Source documentation to verify entry criteria must be reviewed by the Principal Investigator or designee prior to randomization. Source documents from other medical facilities must be located/retrieved during the screening period. Under no circumstances may a subject be randomized in the absence of source documentation including prior qualifying viral load data (as outlined in the Inclusion Criteria).

5.4. Withdrawal and Stopping Criteria

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

A subject may withdraw consent and discontinue participation in this study at any time at his/her own request. The investigator may also, at his or her discretion, discontinue the subject from participating in this study at any time (e.g. safety, behavioral 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. Subjects are not obligated to state the reason for withdrawal. However, a reason for withdrawal 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:

- Virologic withdrawal criteria as specified in Section 5.4 are met;
- For subjects in the TBR arm during the Early Switch Phase, plasma HIV-1 RNA ≥50 c/mL at Week 144 with a confirmatory retest (see Section 5.4)
- Subject is identified as having been mistakenly screened/randomized with exclusionary resistance (see Section 5.2)
- Subject requires substitution or dose modification of DTG, 3TC or any component of their TBR;
- Liver toxicity where stopping criteria met and no compelling alternate cause is identified;
- Renal toxicity are met and no compelling alternate cause is identified;
- Grade 4 clinical or laboratory AE considered causally related to study drug;
- Allergic reaction or Rash criteria are met and no compelling alternate cause is identified.
- Pregnancy (intrauterine), regardless of termination status of pregnancy (Section 7.4.2). As a reminder, females of reproductive potential who change their minds and desire to be pregnant, or who state they no longer are willing to comply with the approved pregnancy avoidance methods, should also be withdrawn from the study.

If a subject is prematurely or permanently withdrawn from the study, the procedures described in the Time and Events Table for the in-clinic Withdrawal visit are to be performed. 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. An in-clinic Follow-Up visit will be conducted 4 weeks after the last dose of study medication for subjects with ongoing AEs, for any serious adverse events (SAEs) regardless of attributability, and also for any laboratory abnormalities that are considered to be AEs or potentially harmful to the subject, at the last on-study visit.

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, three 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 here, wherein the virologic withdrawal criteria are based on the HIV-1 RNA cut-off of 200 c/mL. Clinical management for **precautionary virologic withdrawal (PVW)** criteria are based on consecutive viral loads ≥50 and <200 c/mL.

Suspected Virologic Withdrawal criteria

- one assessment with HIV-1 RNA ≥ 200 c/mL after Day 1 with an immediately prior HIV-1 RNA <50 c/mL

Confirmed Virologic Withdrawal criteria

- one assessment with HIV-1 RNA ≥ 200 c/mL after Day 1 with an immediately prior HIV-1 RNA ≥50 c/mL

Precautionary Virologic Withdrawal criteria

- may be met after two consecutive assessments with HIV-1 RNA ≥50 and <200 c/mL without an identifiable, non-virologic cause (immunization, illness, non-adherence) and after discussion with Medical Monitor, OR
- will be met with three consecutive assessments with HIV-1 RNA ≥50 and <200 c/mL

5.4.1.1. Subjects Meeting Virologic Management Criteria

Subjects with HIV-1 RNA plasma levels ≥50 c/mL at any visit after Day 1 meet "virologic management" criterion and must have plasma HIV-1 RNA levels re-assessed using the algorithm shown in Figure 2. Plasma HIV-1 RNA values determined by the central laboratory only will be used to assess virologic management criteria. Upon notification that a subject's HIV-1 RNA plasma level qualifies him/her as meeting a

"virologic management" criterion, the Investigator should query the subject regarding intercurrent illness, recent immunisation, or interruption of therapy.

All cases meeting "virologic management" criterion must be confirmed by a second measurement performed at least two weeks but not more than 4 weeks apart from the date of the original sample, unless 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 2 to 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 the Medical Monitor to discuss individual subjects, whenever necessary.

5.4.1.2. Managing Subjects Meeting Precautionary Virologic Withdrawal (PVW) or Confirmed Virologic Withdrawal (CVW) Criteria

Once a subject has been confirmed as meeting PVW or CVW criteria, a 'plasma for storage' sample from the earliest viral load ≥200 c/mL [if such is available for a PVW case), or from the SVW visit (if ≥200 c/mL) for a CVW case] 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. Plasma samples for storage also will be obtained at unscheduled visits including the time of a CVW criteria (see Figure 2).

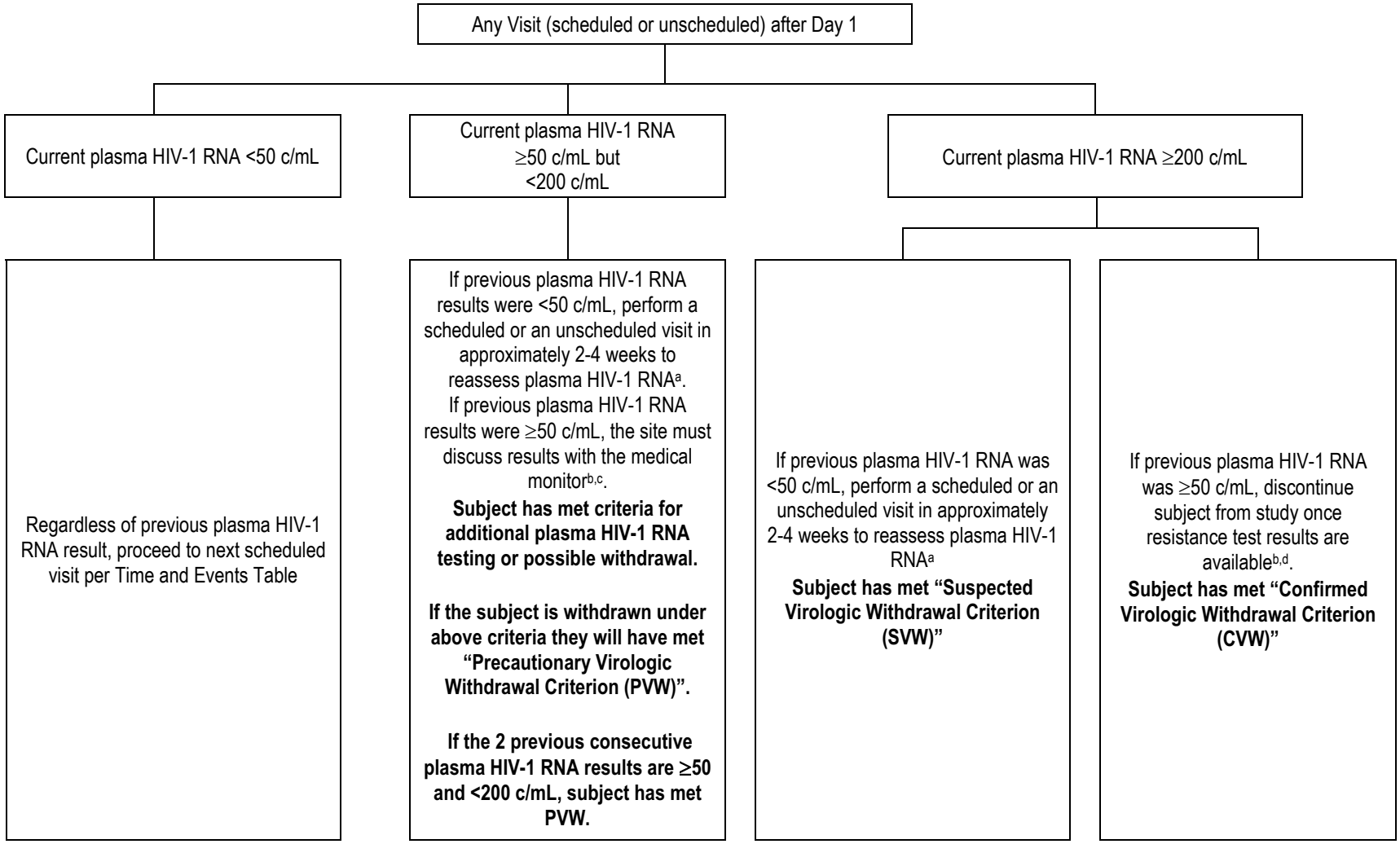
Subjects may continue to receive study drug at the discretion of the investigator until results of resistance testing are available at which time the subject must be discontinued from the study, except in cases where subject samples have HIV-1 RNA <500 c/mL, as noted below. **A subject who meets a PVW or CVW criterion must be discontinued from the study.** Selection of post-study ART regimen for subjects with virologic failure will be recorded in the eCRF.

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, plasma samples will be analysed in an attempt to obtain genotype/phenotype data on samples with HIV-1 RNA ≥200 c/mL, 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 the confirmed HIV-1 RNA level is ≥50 and <200 c/mL, and the decision is taken to withdraw the subject, resistance testing will not be done and the subject should be transitioned off study drug as soon as possible.

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

Figure 2 Criteria for Withdrawal or Re-Assessment of Plasma HIV-1 RNA



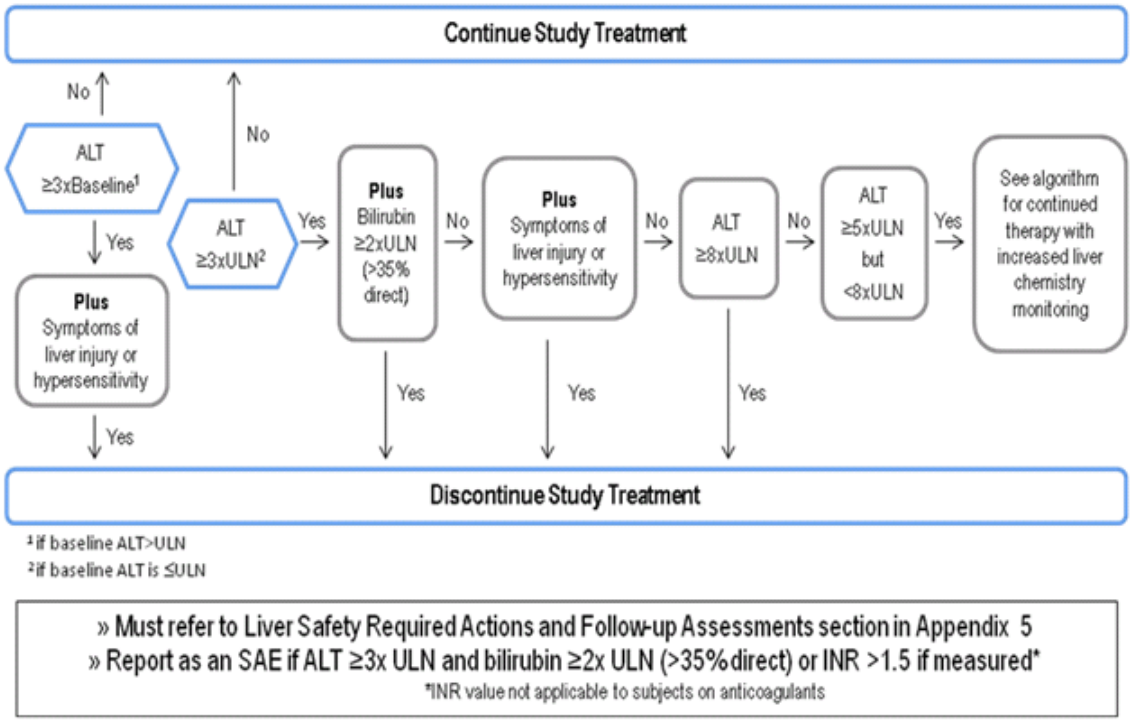
a. Investigators should not schedule reassessment blood draws in the presence of factors that could be associated with virologic blips, such as intercurrent infection, treatment interruption due to toxicity management or non compliance, or vaccination. Subjects should have received full doses of study drug for at least 2 weeks at the time of plasma HIV-1 RNA reassessment.
b. In case of withdrawal, a sample from the initial visit where the HIV-1 RNA plasma level is ≥50 c/mL will be used for resistance testing only if HIV-1 RNA level is ≥200 c/mL. If resistance testing will not be done, withdrawing subjects should be transitioned off study drug as soon as possible.
c. The medical monitor and investigator should consider intercurrent illness, recent immunization, interruption of therapy or other non-virologic reasons associated with transient elevated HIV-1 RNA measurements ≥50 and <200 c/mL. If no non-virologic reasons are identified to explain the lack of virologic suppression, the subject must be withdrawn. If the Investigator and the medical monitor agree that the subject is experiencing a slow re-suppression due to one of the above issues, then a retest HIV-1 RNA measurement is required in approximately 2-4 weeks. If the HIV-1 RNA remains ≥50 c/mL on a second retest (the third consecutive HIV-1 RNA assessment), the subject must be withdrawn.
d. Subjects with confirmed HIV-1 RNA results in the range ≥200 c/mL to <500 c/mL, should be transitioned off study drug and withdrawn from study within 30 days regardless of whether resistance testing has been reported as genotype/phenotype data may not be reliably generated from plasma collected from these subjects.

5.4.2. Liver Chemistry Stopping Criteria

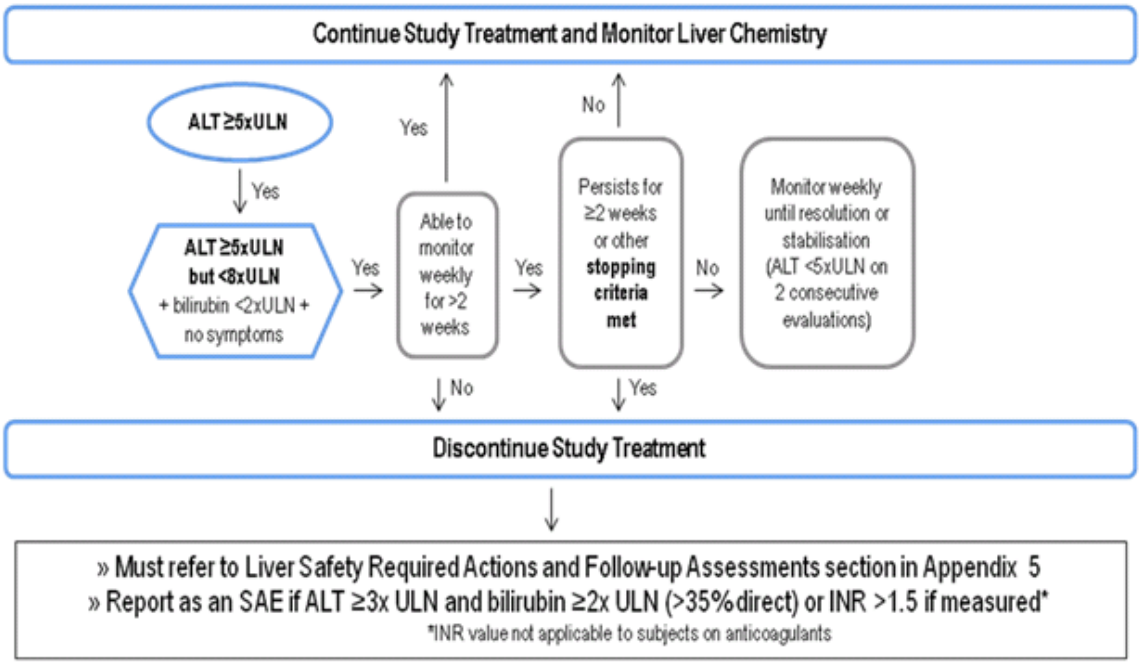
Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

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 Section 13.5.

5.4.2.1. Study Treatment Restart

If subject meets liver chemistry stopping criteria, do not restart subject with study treatment unless:

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

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

Refer to Section 13.6 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 group and completed the Late Switch Phase at the Week 200 visit., and did not enter the Continuation Phase;

- Randomly assigned to either treatment group, completed the Randomized Phase at the Week 200 visit, entered and completed the Continuation Phase, defined as remaining on study until:

    - DTG +3TC FDC tablet is locally approved for use as a 2-drug regimen, and available through public health services or through the subject's usual health insurance payer, 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.

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 serious adverse events (SAEs) and also any laboratory abnormalities that are considered to be AEs or potentially harmful to the subject, at the last on-study visit. 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.

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. All study treatments will be administered at the approved dosages

The investigational study drugs DTG and 3TC will be supplied by GSK/ViiV Healthcare as the fixed dose combination tablet DTG + 3TC. Subjects randomly assigned to continue their TBR for up to 148 weeks will not have drug provided as clinical trial material. The individual components of the TBR will be recorded on the Concomitant ART Therapy (ConART) eCRF page. For subjects randomized to the TBR, provisions will be in place, as needed and after discussion with the study team, to assist patients in obtaining their TBR during the study.

DTG + 3TC must be stored in a secure area under the appropriate physical conditions for the product. Access to and dispensing of the DTG + 3TC FDC will be limited to the investigator and authorized site staff. Study treatment must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol. For further details on storage, access and administration of study treatments, refer to the SRM.

	Study Treatment (Open Label Randomised Phase, Day 1 to Week 200)
Product name:	**DTG + 3TC FDC**
Formulation description:	Clinical Trial Material
Dosage form:	Tablet
Unit dose strength(s)/Dosage level(s):	50mg/300mg
Route of Administration:	Oral
Dosing instructions:	Take one tablet daily.
Physical description:	White, oval, film-coated tablets with 'SV 137' debossed on one face. The tablets are packed in high density polyethylene (HDPE) bottles with induction seals, 2gm desiccant, and child-resistant closures. Each 60mL bottle contains 30 tablets.

6.2. Protocol-Permitted Substitutions

A switch from a PI boosted with RTV to the same PI boosted with cobicistat is allowed. A switch from a PI boosted with cobicistat to the same PI boosted with RTV is allowed.

6.3. 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 randomization schedule. The central randomization schedule will be generated by Pharmaceutical Product Development (PPD) using a validated SAS developed program.

Randomization 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 + 3TC or to the continued TBR arm, in accordance with the computer generated randomization schedule. Each subject will be assigned a unique identifier (designating the subject's randomization code) and a unique treatment number which matches the randomized treatment assignment.

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

6.4. Planned Dose Adjustments

No dose adjustments are permitted in this study for DTG + 3TC or for TBR.

6.5. Blinding

This will be an open-label study and therefore no blinding is required. No summaries of the study data according to actual randomized treatment groups will be available to sponsor staff prior to the planned Week 24 preliminary analysis. Public presentation of the Week 24 analysis will not be done prior to last subject's week 48 visit.

6.6. Packaging and Labeling

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

6.7. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required.

- Only subjects enrolled in the study may receive study treatment and only authorized 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 authorized site staff.
- The investigator, designated site staff, 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/GSK.

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

6.8. Compliance with Study Treatment Administration

When the individual dose for a subject is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

When subjects self-administer study treatment(s) at home, compliance with IP will be assessed through querying the subject during the site visits and documented in the source documents and CRF. Treatment start and stop dates also will be recorded in the CRF.

Additionally, a record of the number of DTG + 3TC tablets dispensed to and taken by each subject must be maintained and reconciled with study treatment and compliance records.

6.9. Treatment of Study Treatment Overdose

For this open-label study, any tablet intake exceeding the randomized daily number of tablets for DTG + 3TC will be considered an overdose [Dolutegravir Product Information, 2017; Epivir Product Information, 2017]. ViiV does not recommend specific treatment for an overdose of DTG + 3TC. As appropriate, the Investigator should use clinical judgment and also refer to the prescribing information for the individual drugs used in the TBR in treating overdose in the TBR arm; ViiV are unable to recommend specific treatment.

For the purposes of this study, an overdose is not an AE unless it is accompanied by a clinical manifestation associated with the overdose. If the clinical manifestation presents with serious criteria, the event is a SAE (see Section 7.4.1). If an overdose occurs and is associated with an adverse event requiring action, all study medications should be temporarily discontinued until the adverse event resolves.

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

- contact the Medical Monitor immediately
- closely monitor the subject for adverse events (AEs)/serious adverse events (SAEs) and laboratory abnormalities until DTG + 3TC can no longer be detected systemically (for at least 2 days).
- obtain a plasma sample for pharmacokinetic (PK) analysis within 60 hours from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis)

- document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

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

6.10. Treatment after the End of the Study

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition. At the end of the study at Week 200, subjects will transition to locally approved and available DTG + 3TC FDC and be managed as per standard of care at their study site. Prior to completion of the Week 200 visit, sites will need to have confirmation that DTG + 3TC FDC is locally available for study subjects. If DTG + 3TC FDC is not yet approved and available locally, ViiV Healthcare will continue to provide study drug in a Continuation Phase until local availability.

Assessments during the Continuation Phase are limited (see Time and Events schedule, Section 7.1).

6.11. 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. or local prescribing information for DTG, 3TC and the subjects' TBR, 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.

6.11.1. Permitted Medications and Non-Drug Therapies

Concomitant medications (prescription and non-prescription) should be prescribed by the relevant health care provider/investigator and administered only as medically necessary during the Randomized and Continuation phases of the study (except prohibited medications described in Section 6.11.2). 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 laboratory tests have been drawn and only when scheduled visits are ≥4 weeks apart. This approach will minimize the risk of non-specific increases in the level of HIV-1 plasma RNA at the next scheduled assessment.

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

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

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

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

6.11.2. 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 6.11.1 for guidance regarding non-HIV vaccines).
- Other experimental agents, ART drugs not otherwise specified in the protocol, cytotoxic chemotherapy, or radiation therapy.
- Systemically administered immunomodulators (such as interleukin and interferon agents) are prohibited through Week 200 (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.
- For participants with an **unanticipated** requirement for HCV therapy during the conduct of the study, the Investigator must consult with the medical monitor. HCV treatment based on interferon or any other medications that have a potential for adverse drug-drug interactions with study treatment, is prohibited during the conduct of the study.
- Acetaminophen is not to be used in patients with acute viral hepatitis [James, 2009].

For a detailed list of prohibited medications, please refer to the SRM.

For information on prohibited medications and drug-drug interactions in relation to other antiretrovirals used in comparator regimens, please consult the latest local prescribing information.

6.11.2.1. Prohibited Medications for Subjects Receiving DTG + 3TC

Medications (or their equivalents) that may cause *decreased* concentrations of DTG and/or 3TC and must not be administered concurrently with DTG + 3TC:

- Carbamazepine
- Oxcarbamazepine
- Phenobarbital
- Phenytoin
- Rifampin
- Rifapentine
- St. John's wort

The following medications are also **prohibited** for subjects receiving DTG:

- **Dofetilide** (DTG may inhibit renal tubular secretion resulting in *increased* dofetilide concentrations and potential for toxicity).
- **Pilsicainide**

Note: Any prohibited medications that decrease dolutegravir 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. 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.

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. Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SRM), which is available on the online Study Web Portal. The SRM will provide the site personnel with administrative and detailed technical information.

7.1. Time and Events Table

7.1.1. Early Switch Phase Time and Events Table (Screening to Week 148)

Procedures	Screening Visit[a]	Open-label Randomised Early Switch Phase														Switch Visit	Withdrawal	Follow-up[d]
		Baseline / Day 1	Week															
			4	8	12	24	36	48	60	72	84	96	108 (optional)[b]	120	132 (optional)[b]	144	148[c]	
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																	
Body Weight (BMI will be calculated within the eCRF)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	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	
Columbia Suicidality Severity Rating Scale		X[h]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	

Procedures	**Screening Visit**[a]	**Open-label Randomised Early Switch Phase**															**Switch Visit**	**Withdrawal**	**Follow-up**[d]
		Baseline / Day 1	**Week**																
			4	**8**	**12**	**24**	**36**	**48**	**60**	**72**	**84**	**96**	**108 (optional)**[b]	**120**	**132 (optional)**[b]	**144**	**148**[c]		
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Symptom Directed Physical Exam[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
12-lead ECG[j]	X																		
Adverse events		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
Willingness to Switch[l]		X[l]																	
EQ-5D-5[m]		X	X			X		X				X				X		X	
Laboratory Assessments																			
Quantitative plasma HIV-1 RNA[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Lymphocyte subset (CD4+ at all visits and CD8+ at Baseline, and Weeks 24, 48, 96, 144 and 196 only)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Plasma for storage[o]	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
Hematology	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[p]		X				X		X				X				X		X[q]	
Urinalysis and spot urine for protein analysis[r]		X				X		X				X				X		X	X
Pregnancy test[s,t,u]	S	U/S[v]	S	S	S	S	S	S	S	S	S	S	S	S	S	S	U	S	

Procedures	**Screening Visit**[a]	**Open-label Randomised Early Switch Phase**															**Switch Visit**	**Withdrawal**	**Follow-up**[d]
		Baseline / Day 1	**Week**																
			4	**8**	**12**	**24**	**36**	**48**	**60**	**72**	**84**	**96**	**108 (optional)**[b]	**120**	**132 (optional)**[b]	**144**	**148**[c]		
HbsAg, anti-HBc, anti-HBs, and HBV DNA[w]	X																		
HCV antibody	X																		
RPR	X																		
Insulin, HbA1c and renal, and bone marker analytes (blood/urine)[x]		X				X		X				X				X		X[q]	
Whole Blood (Virology)[y]		X						X				X				X		X	
Whole Blood (Telomere length)[z]		X						X				X				X		X[aa]	
Cryopreserved PBMCs[bb]		X						X				X				X		X[aa]	
Inflammation biomarkers (Blood)[cc]		X						X				X				X		X[aa]	
Study Treatment																			
IVRS/IWRS[dd]	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		
Study treatment accountability (pill counts)			X	X	X	X	X	X	X	X	X	X		X		X		X	
Pharmacokinetic[ee]																			
Intensive PK sample collection at selected sites for subset of ~30 subjects (Fasting)[ee]			X[ff]																

Procedures	Screening Visit[a]	Open-label Randomised Early Switch Phase														Switch Visit	Withdrawal	Follow-up[d]
		Baseline / Day 1	Week 4	8	12	24	36	48	60	72	84	96	108 (optional)[b]	120	132 (optional)[b]	144	148[c]		
Dispense PK Diary Card to intensive PK sub-set		X																	
Sparse PK sample collection[ee]			X[gg]	X	X	X	X	X											
Dispense PK Diary Card to Sparse PK subjects		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, HbA1c = Glycated hemoglobin, HBsAg = hepatitis B surface antigen, HCV = hepatitis C virus, HIV-1 = human immunodeficiency virus type 1, IVRS = interactive voice recognition system, IWRS = interactive web recognition system, PBMC = peripheral blood mononuclear cell, RNA = ribonucleic acid, RPR = rapid plasma reagin

7.1.2. Late Switch Phase Time and Events Table: TBR subjects who switched to DTG + 3TC at Week 148

TBR subjects switching at Week 148 are followed up at 4, 12 and 24 weeks post-switch after which 24 weekly visits are resumed.

Procedures	Late Switch Phase through End of Study						Continuation Phase	Withdrawal	Follow-up
	Week 152	160	172	184 (optional)[b]	196	200[hh]	Every 24 weeks after Week 200[b,ii]		
Clinical and Other Assessments									
Body Weight (BMI will be calculated within the eCRF)	X	X	X	X	X	X	X	X	X
HIV associated conditions	X	X	X	X	X	X	X	X	
Columbia Suicidality Severity Rating Scale	X	X	X	X	X		X	X	

Procedures	**Late Switch Phase through End of Study**						**Continuation Phase**	**Withdrawal**	**Follow-up**
	Week								
	152	**160**	**172**	**184 (optional)[b]**	**196**	**200[hh]**	**Every 24 weeks after Week 200[b,ii]**		
Concomitant medication	X	X	X	X	X	X	X	X	X
Symptom Directed Physical Exam[i]	X	X	X	X	X	X		X	X
Adverse events	X	X	X	X	X	X	X	X	X
Serious adverse events	X	X	X	X	X	X	X	X	X
EQ-5D-5L[m]					X			X	
Laboratory Assessments									
Quantitative plasma HIV-1 RNA[n]	X	X	X	X	X		X	X	
Lymphocyte subset (CD4+ at all visits and CD8+ at Baseline, and Weeks 24, 48, 96, 144 and 196 only)	X	X	X	X	X			X	
Plasma for storage[o]	X	X	X	X	X		X	X	
Clinical chemistry	X	X	X	X	X	X		X	X
Hematology	X	X	X	X	X	X		X	X
Fasting lipids and glucose[p]					X			X[q]	
Urinalysis and spot urine for protein analysis[r]					X			X	X
Pregnancy test[s,t,u]	S	S	S	S	S	S	S	S	
Insulin, HbA1c and renal, and bone marker analytes (blood/urine)[x]					X			X[q]	
Whole Blood (Virology)[y]					X			X	
Whole Blood (Telomere length)[z]					X			X[aa]	
Cryopreserved PBMCs[bb]					X			X[aa]	
Inflammation biomarkers (Blood)[cc]					X			X[aa]	
Study Treatment									
IVRS/IWRS[dd]	X	X	X	X	X	X	X	X	X
Dispense study treatment	X	X	X		X		X		

Procedures	Late Switch Phase through End of Study						Continuation Phase	Withdrawal	Follow-up
	Week								
	152	160	172	184 (optional)[b]	196	200[hh]	Every 24 weeks after Week 200[b,ii]		
Study treatment accountability (pill counts)	X	X	X		X	X	X	X	

7.1.3. Late Switch Phase Time and Events Table: DTG + 3TC arm

Procedures	Late Switch Phase through End of Study					Continuation Phase	Withdrawal	Follow-up
	Week							
	160 (optional)[b]	172	184 (optional)[b]	196	200[hh]	Every 24 weeks after Week 200[b,ii]		
Clinical and Other Assessments								
Body Weight (BMI will be calculated within the eCRF)	X	X	X	X	X	X	X	X
HIV associated conditions	X	X	X	X	X	X	X	
Columbia Suicidality Severity Rating Scale	X	X	X	X		X	X	
Concomitant medication	X	X	X	X	X	X	X	X
Symptom Directed Physical Exam[i]	X	X	X	X	X		X	X
Adverse events	X	X	X	X	X	X	X	X
Serious adverse events	X	X	X	X	X	X	X	X
EQ-5D-5L[m]				X			X	
Laboratory Assessments								
Quantitative plasma HIV-1 RNA[n]	X	X	X	X		X	X	
Lymphocyte subset (CD4+ at all visits and CD8+ at Baseline, and Weeks 24, 48, 96, 144 and 196 only)	X	X	X	X			X	
Plasma for storage[o]	X	X	X	X		X	X	

Procedures	**Late Switch Phase through End of Study**					**Continuation Phase**	**Withdrawal**	**Follow-up**
	Week							
	160 (optional)[b]	**172**	**184 (optional)[b]**	**196**	**200[hh]**	**Every 24 weeks after Week 200[b,ii]**		
Clinical chemistry	X	X	X	X	X		X	X
Hematology	X	X	X	X	X		X	X
Fasting lipids and glucose[p]				X			X[q]	
Urinalysis and spot urine for protein analysis[r]				X			X	X
Pregnancy test[s,t,u]	S	S	S	S	S	S	S	
Insulin, HbA1c and renal, and bone marker analytes (blood/urine)[x]				X			X[q]	
Whole Blood (Virology)[y]				X			X	
Whole Blood (Telomere length)[z]				X			X[aa]	
Cryopreserved PBMCs[bb]				X			X[aa]	
Inflammation biomarkers (Blood)[cc]				X			X[aa]	
Study Treatment								
IVRS/IWRS[dd]	X	X	X	X	X	X	X	X
Dispense study treatment		X		X		X		
Study treatment accountability (pill counts)		X		X	X	X	X	

a. As soon as all Screening results are available, randomization may occur.
b. This optional study visit is ONLY to be conducted in countries that require visits every 3 months per standard of care.
c. Subjects with plasma HIV-1 RNA ≥50 c/mL at Week 144 must have HIV-1 RNA level re-assessed by a second measurement performed 2-4 weeks later. Subjects should have received full doses of study treatment for at least 2 weeks at the time of HIV-1 RNA re-assessment. Subjects randomized to DTG + 3TC do not attend a Week 148 switch visit.
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. Only the laboratory tests necessary to evaluate the AE/SAE/laboratory abnormality should be collected.
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. Genotypic resistance testing results MUST be provided to ViiV after screening and before randomization.
f. Full medical history will be conducted prior to randomization 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. BMI will be calculated within the eCRF.
h. On Day 1, the electronic Columbia Suicidality Severity Rating Scale eC-SSRS, patient completed questionnaire) is to be administered prior to randomization.

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/GSK product will be collected between obtaining informed consent and administration of study drug at Day 1.
l. Willingness to Switch Survey must be done prior to randomization.
m. Questionnaire/Surveys are recommended to be administered at the beginning of the visit before any other assessments are conducted. Only conduct questionnaires/surveys at Withdrawal if occurring prior to Week 196.
n. See Virologic Withdrawal and Stopping Criteria Section of protocol (Section 5.4).
o. Plasma samples for storage will be collected at each visit starting at Screening, including unscheduled visits (e.g. for HIV-1 RNA levels and immunological parameters). These samples will be used when needed such as when samples are lost, arrive at the laboratory unevaluable, or for genotypic and/or phenotypic analyses when subjects meet Suspected and Confirmed Virologic Withdrawal criteria.
p. An overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable.
q. Collect sample for these assessments ONLY if the Withdrawal visit occurs at Week 24, 48, 96, 144 or 196.
r. A morning specimen is preferred. To assess renal biomarkers: urine albumin/creatinine ratio; urine protein/creatinine ratio; and urine phosphate.
s. Women of childbearing potential only. S=serum, U=urine. Pregnancy events will be captured starting at Day 1 following exposure to study drug.
t. Remind females of reproductive potential of the need to avoid pregnancy while in study and adherence to the study's contraception requirements.
u. Beginning after Week 96, if study visits are every 24 weeks, participants who are women of child bearing potential must also do a home-based urine pregnancy test approximately every 12 weeks between study visits at approximately Weeks 108, 132, 160 and 184 and during the Continuation Phase. Site staff must contact the participants who are women of child bearing potential to remind them to complete the test and to verify and record pregnancy test results in the source documents. The site must also complete the pregnancy status eCRF if a pregnancy occurs and report the pregnancy to ViiV/GSK per Section 13.3.2.
v. Local serum pregnancy test on Day 1 is allowed if it can be done, and results obtained, within 24 hours prior to randomization
w. 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.
x. Blood sample for insulin, HbA1c, and renal and bone biomarker assessments: **Renal:** Cystatin C; Beta-2-Microglobulin; Retinol Binding Protein (RBP); **Bone:** bone specific alkaline phosphatase, procollagen type 1-N-propeptide, type 1 collagen cross-linked C-telopeptide, osteocalcin, 25 hydroxy-Vitamin D.
y. Whole blood (Virology) may be used for virologic analyses as described in the protocol.
z. Whole blood will be used for telomere length evaluation at Day 1, Week 48, Week 96, Week 144, Week 196 and at the Withdrawal visit.
aa. Collect sample for these assessments ONLY if the Withdrawal visit occurs at Week 48, 96, 144 or 196
bb. PBMCs will be collected, cryopreserved and stored in a subset of sites. These samples will be used for the measurement of telomerase activity.
cc. Blood sample for inflammation biomarker assessments: IL-6, hs-CRP, d dimer, sCD14, sCD163.
dd. At Screening, a subject number will be generated.
ee. PK sampling in subjects from the DTG/3TC FDC arm only, as detailed in Section 11.
ff. Intensive PK sampling in a subset of subjects from the DTG/3TC FDC arm at select sites at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 10 and 24 hours post-dose. On the intensive PK day, patients are required to fast from 8 hours prior to dosing and then through 4 hours post-dose. Detailed in Section 11.
gg. At Week 4, subjects who performed intensive PK do not perform Sparse PK sampling.
hh. Subjects must return to the clinic for a Week 200 End of Study visit when transitioning to commercial supplies or to an alternate ART regimen, if appropriate. Do not dispense

study treatment at this study completion visit unless the participant is entering the Continuation Phase.

ii. Only in case of non-availability of DTG + 3TC FDC. 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.

7.2. Screening and Critical Baseline Assessments

Written informed consent must be obtained from each potentially eligible subject 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 enrollment 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 PPD.

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5. If they are being utilised in the study, Patient Reported Outcomes questionnaires should be completed by subjects before any other assessment at a clinic visit, in the order specified.

7.2.1. Screening Assessments

Eligibility criteria must be assessed carefully 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 Baseline 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. Background information to be collected at Screening includes demography (year of birth, sex, race and ethnicity) and prior ART history.

Eligible subjects may be randomly assigned immediately 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 prior to Baseline (Day 1) during which all clinical and laboratory assessments of eligibility must be performed and reviewed. The Screening period of up to 28 days is to accommodate availability of all Screening assessment results, completion of source document verification to satisfy the Inclusion and Exclusion Criteria including the required previous HIV-1 RNA values, and scheduling. All Screening results **must** be available prior to randomization.

All information about the subject's current and any past regimen must be available for review by the Principal Investigator or designee prior to randomization. Source documents from other medical facilities must be located/received during the 28 day screening period and under no circumstances may the subject be randomized in the absence of source documentation, even if there are delays in receipt of this information. A subject may be re-screened if the source documentation is obtained after the screening window closes.

Details regarding prior resistance data must be noted in the source documentation and eCRF. Resistance testing reports with genotypic data **must** be provided to ViiV after screening and before randomization for review by ViiV. Sites must wait for the study virologists to confirm the lack of exclusionary resistance mutations, which will be provided to the site before the screening window closes. Details for tracking historic

resistance report availability and sending to ViiV Virology for evaluation are described in the SRM. Details regarding baseline or prior resistance data must be noted in the source documentation. **If a subject is identified as having been mistakenly screened/randomized with exclusionary resistance, they will be withdrawn.**

Subjects with chronic active hepatitis B are excluded. Evidence of Hepatitis B virus (HBV) infection is based on the results of testing at Screening for Hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), hepatitis B surface antibody (anti-HBs), and HBV DNA. HBV DNA testing will only be performed for subjects with positive anti-HBc and negative HbsAg and negative anti-HBs (past and/or current evidence).

All subjects will be screened for syphilis at screening. Subjects with untreated syphilis infection, defined as a positive Rapid Plasma Reagin (RPR) without clear documentation of treatment, are excluded unless they complete treatment during the 28-day screening window and 7 days prior to randomization. Subjects who complete treatment after the screening window closes may be rescreened.

Subjects who meet all entry criteria are randomized and assigned a randomization number. 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 or for a viral load ≥ 50c/mL at time of screening. Subjects who are randomized into the trial and subsequently withdrawn from the study for any reason may not be rescreened.

7.2.2. Baseline Assessments

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

Other baseline information to be collected at Day 1 includes general medical history and current medical conditions. Laboratory and health outcomes assessments will also be assessed. Questionnaire/surveys are recommended to be administered at the beginning of the visit before any other assessments are conducted.

7.3. Efficacy

7.3.1. Efficacy Evaluations

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 lower limit of quantitation 40 c/mL. In some cases (e.g., where the plasma HIV-1 RNA is below the lower limit of detection for a given assay) additional exploratory methods may be used to further characterize plasma HIV-1 RNA levels.

Lymphocyte Subsets

Lymphocyte subsets will be collected for assessment by flow cytometry (total lymphocyte counts, percentage, and absolute CD4+ and CD8+ lymphocyte 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 Revised Classification System for HIV Infection in Adults (see Section 13.7). When assessing CDC stage at screening consider only the latest available CD4 T-cell count, including CD4 T-cell count at screening. If a stage-3–defining opportunistic illness has been diagnosed up to screening, then the stage is 3 regardless of CD4 T-cell count test results.

For Baseline CDC classification at Day 1 use latest CD4 T-cell count, including CD4 T-cell count at baseline. If a stage-3–defining opportunistic illness has been diagnosed between screening and Day 1, then the stage is 3 regardless of CD4 T-cell count test results.

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.

7.3.1.1. Primary Efficacy Endpoint

The primary endpoint will be the proportion of subjects with virologic failure endpoint as per FDA snapshot category at week 48 for the ITT-E population.

7.3.1.2. Secondary Efficacy Endpoints

- Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Weeks 24,48, 96 and 144 using the Snapshot algorithm for the ITT-E population
- Percentage of subjects with viral failure endpoint as per FDA snapshot category at Weeks 24, 96 and 144
- Change from Baseline in CD4+ lymphocyte count at Weeks 24, 48, 96, and 144
- Change from Baseline in CD8+ lymphocyte count and CD4+/CD8+ cell counts ratio at Weeks 24, 48, 96 and 144
- Incidence of disease progression (HIV-associated conditions, AIDS and death).

7.3.1.3. Exploratory Efficacy Endpoints

- Proportion of subjects with plasma HIV-1 RNA <50 c/mL by patient subgroup(s) (e.g., by age, gender, Baseline CD4+) at Week 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, 144 and 196 by patient subgroups

Additional exploratory efficacy endpoints for subjects treated with DTG + 3TC since the Early Switch Phase, and for subjects switching in the Late Switch Phase include:

- Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 196 using the Snapshot algorithm for the ITT-E population
- Change from Baseline in CD4+ and CD8+ lymphocyte count and CD4+/CD8+ cell counts ratio at Week 196
- Incidence of disease progression (HIV associated conditions, AIDS and death) through Week 196.

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 Section 13.8.

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/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 at the timepoints specified in the Time and Events Table.
- 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 ViiV/GSK within 24 hours, as indicated in Section 13.8.
- 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 ViiV/GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to ViiV/GSK are provided in Section 13.8

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, and non-serious AEs of special interest will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.

7.4.1.4. Cardiovascular and Death Events

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

The CV CRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific CV 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 (Section 13.7) 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/GSK as AEs and SAEs even though such event or outcome may meet the definition of an AE or SAE, **unless the following conditions apply**:

- The investigator determines that the event or outcome qualifies as an SAE under part 'f' of the SAE definition (see Section 13.8.2), 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/GSK (or designee) of SAEs related to study treatment (even for non- interventional post-marketing studies) 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 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 will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

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

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

7.4.2. Pregnancy

Information on the occurrence of pregnancies in female subjects will be collected over the period starting at Screening and ending at the final Follow-up visit. Pregnancies that occur following the first dose of study drug will be reported to the Medical Monitor. Follow-up information will be collected for pregnancies occurring from Day 1 to the final Follow-up visit. Beginning after Week 96, if study visits are 24 weeks apart, participants who are women of child bearing potential must also do a home-based urine pregnancy test approximately every 12 weeks between study visits at approximately Weeks 108, 132, 160 and 184. Site staff must contact the participants who are women of child bearing potential to remind them to complete the test and to verify and record pregnancy test results in the source documents. Site staff must complete the pregnancy status eCRF if a pregnancy occurs. If a pregnancy is reported then the investigator should inform ViiV/GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Section 13.3.2.

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

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child(ren). Pregnancy

complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as SAEs.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment must be reported promptly to ViiV/GSK (or designee).

GSK's central safety department will forward this information to the ART Pregnancy Registry. The international registry is jointly sponsored by manufacturers or licensees of ARV products. Additional information and a list of participating manufacturers/licensees are available from http://www.apregistry.com/.

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. Vital Signs

At the Screening visit, vital signs will be measured in semi-supine position after 5 minutes rest and will include height, weight, systolic and diastolic blood pressure and Body Mass Index (BMI). Body weight and BMI will also be assessed at each visit according to the Time and Events Table (Section 7.1).

7.4.5. Electrocardiogram (ECG)

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

7.4.6. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Section 7.1, must be performed by central laboratory services, with the exception of exceptional circumstances during screening noted in Section 5.3. Laboratory assessments must be conducted in accordance with the Central 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 the central laboratory and are detailed in the laboratory manual. Reference ranges for all safety parameters will be provided to the site by the central laboratory.

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. AE, SAE or dose modification) the results must be recorded in the eCRF. Local laboratory services may be used to verify pending laboratory parameters only after consultation and agreement with the study team.

Refer to the lab manual 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. Labs will be graded automatically by the central lab according to the DAIDS toxicity scales (See Section 13.9 “Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events”).

Table 1 Protocol Required Safety Laboratory Assessments

Hematology:			
Platelet count		Automated WBC differential:	
RBC count		Neutrophils	
WBC count (absolute)		Lymphocytes	
Hemoglobin		Monocytes	
Hematocrit		Eosinophils	
MCV		Basophils	
MCH			
Clinical Chemistry:			
BUN	Potassium	AST	Total bilirubin[a]
Creatinine	Chloride	ALT	Albumin
Glucose[b]	Total CO2	Alkaline phosphatase	Creatine phosphokinase
Sodium		Phosphate	GFR/Creatinine clearance[c]
Calcium		Protein	Cystatin-C (Day 1 only)
Fasting Lipid Panel[d]			
Total cholesterol			
HDL cholesterol			
LDL cholesterol			
Triglycerides			
Urinalysis			
specific gravity, pH, glucose, protein, blood and ketones by dipstick (with microscopic examination if blood or protein is abnormal), urine albumin/creatinine ratio, urine protein/creatinine ratio, urine phosphate			
Other Tests			
Plasma HIV-1 RNA[e]			
CD4+ lymphocyte counts and percent			
CD8+ lymphocyte counts, percent and CD4+/CD8+ cell count ratio at Baseline and Weeks 24, 48, 96, 144 and 196			
Hepatitis B (HBsAg, anti-HBc, anti-HBs, HBV DNA)			
Hepatitis C (anti-HCV)			
PT/INR			
Pregnancy test for women of childbearing potential[f]			
Renal biomarkers including Cystatin-C (blood), Retinol Binding Protein (RBP, blood/urine); and Beta-2-Microglobulin (B2M, blood/urine)[g]			
Bone biomarkers including: Bone-specific alkaline phosphatase, procollagen type 1 N-propeptide, type 1 collagen cross-linked C-telopeptide, osteocalcin, 25 hydroxy-Vitamin D[g]			
Inflammation biomarkers including IL-6, hs-CRP, d dimer, sCD14 and sCD163[g]			
HbA1c, Insulin, HOMA-IR			

MCV = mean corpuscular volume, RBC = red blood cells, WBC = white blood cells, BUN = Blood urea nitrogen, AST=aspartate aminotransferase, ALT = alanine aminotransferase, CO_2 = carbon dioxide, HDL = high density lipoprotein, LDL = low density lipoprotein, HbsAg= hepatitis B virus surface antigen, PT/INR = prothrombin time/international normalized ratio, HbA1c = glycated haemoglobin, HOMA-IR = homeostasis model of assessment – insulin resistance, Il-6 = interleukin-6, hs-CRP = high-sensitivity C reactive protein, sCD = soluble CD.

a) Direct bilirubin will be reflexively performed for all total bilirubin values >1.5 × ULN.
b) For fasting glucose assessments, an overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable for subjects with afternoon appointments.
c) Glomerular filtration rate (GFR) will be estimated by the central laboratory using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI-creatinine) [Levey, 2009]. In addition, GFR will be estimated by the central laboratory using the CKD-EPI-cystatin C [Inker, 2012] at day 1 and when indicated by renal toxicity criteria.
d) For fasting lipids assessments, an overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable for subjects with afternoon appointments.
e) For subjects meeting virologic withdrawal criteria, plasma samples will be analyzed in attempt to obtain

genotype/phenotype data.

f) Urine pregnancy test/ serum pregnancy test will be performed according to the Time and Events Table.

g) The intention is to utilize these biomarker data for research purposes; the sponsor will not be reporting real-time results of these assessments to the investigator, except for Cystatin C (Day 1 only) and 25 hydroxy-Vitamin D.

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 etiology should be identified and the sponsor notified.

7.4.7. Suicidal Risk Monitoring

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

Subjects should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior. It is recommended that the investigator consider mental health consultation or referral for subjects who experience signs of suicidal ideation or behavior. 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 behavioral suicidal events used in this scale are based on those used in the Columbia Suicide History Form [Posner, 2007]. Questions are asked on suicidal behavior, suicidal ideation, and intensity of ideation. Day 1 (Baseline) visit questions will be in relation to lifetime experiences and current experiences (within the past 2 months); all subsequent questioning is in relation to the last assessment. The eC-SSRS is to be administered as a patient completed questionnaire specified in the Time and Events Table. 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 behavior, a suicide attempt, or a completed suicide. The investigator will exercise his or her medical and scientific judgment in deciding whether an event is possibly suicide-related. PSRAE forms should

be completed and reported to ViiV/GSK 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. In addition to measurements of serum creatinine, estimated GFR, and urinary excretion of albumin, protein, creatinine and phosphate, additional renal biomarkers include:

Renal biomarkers:

- Cystatin C (blood),
- Retinol Binding Protein (RBP, blood/urine)
- Beta-2-Microglobulin (B2M, blood/urine).

Bone biomarkers:

- Bone-specific alkaline phosphatase
- Procollagen type 1 N-propeptide
- Type 1 collagen cross-linked C-telopeptide
- Osteocalcin
- 25 hydroxy-Vitamin D

Blood is being collected to perform assessments of insulin resistance, biomarkers of inflammation and telomere function.

Inflammation biomarkers:

- Interleukin-6 (IL-6)
- High-sensitivity C reactive protein (hs-CRP)
- D-dimer
- Soluble CD14 (sCD14)
- Soluble CD163 (sCD163)

Insulin, HbA1c, and HOMA-IR

Telomere function:

- Whole blood will be used for measurement of telomere length.
- In a subset of sites, PBMCs will be collected, cryopreserved and stored for measurement of telomerase activity.

Since the intention is to utilize these biomarkers for research purposes and the clinical significance of these results is uncertain, the Sponsor will not be reporting real time results of these assessments to the investigator except for Cystatin C (Day 1 only) and 25 hydroxy-vitamin D.

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 (for potential viral genotypic

and phenotypic analyses). 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 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

Details concerning the handling, labeling and shipping of these samples will be supplied separately. 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 assays.

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

7.6.1. HIV-1 Exploratory Analysis

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

7.7. Value Evidence and Outcomes

Health outcomes assessments will be conducted according to the Time and Events Table (Section 7.1). Assessments are recommended to be administered at the beginning of the visit prior to collection of blood for analysis and other scheduled assessments. Questionnaires will be administered on paper except the willingness to switch survey, which will be a verbal question.

The following 2 health outcomes assessments will be utilized in this study:

To assess the reason(s) for their participation and facilitate an understanding of subject's willingness to switch, subjects will be asked a single item question prior to randomization.

The European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L), developed by EuroQol group, is a standardized, 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 analog scale (VAS) that assesses overall health [Herdman, 2011].

7.8. Pharmacokinetic Assessments

A PK substudy will be performed (see Section 11 for details).

8. DATA MANAGEMENT

- For this study, electronic Data Management (eDM) subject data will be entered into GSK/PPD 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 GSK/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 (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.
- CRFs (including queries and audit trails) will be retained by ViiV/GSK/PPD, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to ViiV/GSK according to GSK/PPD policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

This study is designed to show that the antiviral effect of switching to a simplified two-drug regimen of DTG + 3TC once-daily is not inferior to continuation of their TBR at week 48 in HIV-1 infected ART-experienced subjects.

Non-inferiority can be concluded if the upper bound of a two-sided 95% confidence interval for the difference in virologic failure rates between the two treatment arms is smaller than 4%. If r_d is the virologic failure rate on DTG + 3TC and r_f is the virologic failure rate on the current ART regimen, then the hypotheses can be written as follows:

$$H_0: r_d - r_f \geq 4\% \qquad H_1: r_d - r_f < 4\%$$

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

Assuming a true 2% virologic failure rate in each arm, a non-inferiority margin of 4%, and a 2.5% one-sided significance level, this study requires 275 subjects per treatment arm.

This would provide 92% power to show non-inferiority for the proportion of subjects with virologic failure according to the FDA snapshot algorithm at 48 weeks post-switch. If we observed a 2% virologic failure rate for the non-switch subjects then non-inferiority would be declared if the observed treatment difference was less than or equal to 1.3 percentage points.

While the targeted study size was 550 randomised subjects (from a target of 800 screened subjects), the study was over-enrolled based on an unexpected surge in recruitment in the last week of screening, resulting in a total of 743 subjects randomized.

This final sample size will provide 97.3% power to show non-inferiority with the current assumptions, and non-inferiority can be declared if the actual observed treatment difference in the trial is less than or equal to 1.6%.

9.2.1.1. Rationale for non-inferiority margin

According to the FDA's 2015 guidance document (Human Immunodeficiency Virus-1 Infection: Development of ART Drugs for Treatment, November 2015), the margin for switch trials is driven by the largest clinically tolerable virologic failure rate. Per the FDA document, typical rates of virological failure seen in switch studies range from 1 to 3 percent and a margin of 4% for virologic failure rate is considered tolerable. Assuming 2% virologic failure rate in both treatment arms, a 4% non-inferiority margin is considered comparable to a 10% to 12% non-inferiority margin using response rate as

endpoint. A margin of 4% was therefore chosen for the present study assuming 2% failure rate in both arms [CDER, 2015].

9.2.1.2. Response and Virologic Failure rate assumptions

Table 2 shows Snapshot response (HIV-1 RNA <50 c/mL) rates and Snapshot virologic failure (HIV-1 RNA ≥50 c/mL) rates in previous switch studies in HIV-1 infected ART-experienced subjects. Taken together, these data suggest that a reasonable assumption for the true failure rate for the current ART control arm and the switch arm is 2%.

Table 2 Snapshot Response and Virologic Failure rates in previous switch studies

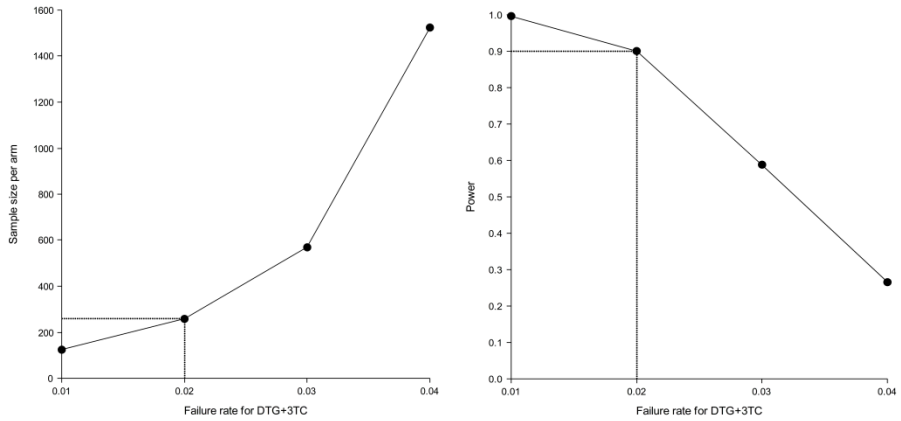
Week 48			
Study	**Treatment Arm**	**Response rate (HIV-1 RNA <50 c/mL)**	**Virologic Failure (HIV-1 RNA ≥50 c/mL)**
SPIRIT[a,b]	RPV/FTC/TDF	89%	8/317 (2.5%)
STRATEGY-PI[c]	QUAD	94%	2/290 (<1%)
	PI + FTC/TDF	87%	2/139 (1%)
STRATEGY-NNRTI[d]	QUAD	93%	3/290 (1%)
	NNRTI + FTC/TDF	88%	1/143 (<1%)
SALT[e]	ATV/r+3TC	77%	Not available[f]
	ATV/r+2NRTIs	76%	Not available[f]
OLE[g]	LPV/r+3TC	88%	Not available[h]
	LPV/r+TDF/FTC or ABC/3TC	87%	Not available[h]
GS-292-0109[i]	E/C/F/TAF	97%	10/959 (1%)
	TDF-based regimen[j]	93%	6/477 (1%)
GS-US-311-1089[k]	TAF containing regimen	94%	1/333 (<1%)
	TDF regimen	93%	5/330 (2%)
SWORD 1 & 2[l]	CAR	95%	6/511 (1%)
	DTG+RPV	95%	3/513 (<1%)
Week 24			
STRIIVING[m]	DTG + ABC/3TC STR	85%	1%
	Current ART	88%	1%

a. [Palella, 2014]
b. Participants in the PI/r +2 NRTIs arm were switched to RPV/FTC/TDF at Week 24; therefore Week 48 response data are not available for this treatment group.
c. [Arribas, 2014]
d. [Pozniak, 2014]
e. [Perez-Molina, 2015]
f. The percentage of snapshot virologic failure is not available; however, 4% in the dual arm and 3% in the cART arm had protocol defined virologic failure (PDVF).
g. [Arribas, 2015]
h. The percentage of snapshot virologic failure is not available; however, 2% per arm had PDVF.
i. [Mills, 2016]
j. EVG/Cobistat/TDF/FTC, EFV/TDF/FTC, ATV/Cobistat/TDF/FTC, or RTV/ATV/TDF/FTC
k. [Gallant, 2016]
l. [Libre, 2017]
m. [Trottier, 2015]

9.2.2. Sample Size Sensitivity

Figure 3 shows sensitivity of the required sample size to the true response rate for the DTG + 3TC arm assuming a 2% failure rate in the current ART non-switch arm and a 4% margin.

Figure 3 Sample size sensitivity for the Snapshot Virologic Failure



Power=90%, NI margin=4%, control arm failure rate=2% N=275 per arm, NI margin=4%, control arm failure rate=2%

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 randomized subjects who receive at least one dose of study medication. Subjects will be assessed according to their randomized 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 significant 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 analyzed according to the actual treatments received. Unless otherwise stated, the Safety Population will be used for safety analyses.

9.3.2. Analysis Data Sets

The primary analysis set of data is based on virologic failure defined by the FDA snapshot algorithm. With the exception below, virologic failure includes subjects who changed any component of background therapy to a new drug class, changed background components that were not permitted per protocol, or changed any background drug in the regimen because of lack of efficacy (perceived or documented) before Week 48; patients who discontinued study drug or study before Week 48 for lack or loss of efficacy and patients who are equal to or above 50 c/mL in the 48-week window.

A secondary analysis set of data is based on subjects' responses at <50 c/mL calculated according to the FDA 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 (with the exception below) are allowed in the protocol.

Note: A switch from a PI boosted with ritonavir to the same PI boosted with cobicistat (and vice versa) is permitted per protocol and will not be considered as a change in background ART hence, will not incur a penalty in the Snapshot algorithm, regardless of reason or date of switch, as these agents are expected to have similar boosting effect and no impact on overall efficacy of the regimen.

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 (to be specified in the RAP). Full details of this snapshot algorithm will be contained in the RAP.

Another secondary set of data will treat 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, which uses only data that are available at a particular time point with no imputation for missing values, will be the primary dataset for assessing safety and will also be used for some analyses of efficacy and health outcomes.

Further details will be provided in the RAP.

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 virologic failure dataset. The primary comparison will be made at a one-sided 2.5% level of

significance. Treatment with DTG + 3TC will be declared non-inferior to the TBR if the upper bound of a two-sided 95% confidence interval for the difference between the two groups in virologic failure rates at Week 48 lies below 4%.

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 + 3TC is superior to the TBR treatment will be tested using the same level of significance as for the tests of non-inferiority. Superiority will be declared if the upper bound of the confidence internal is below 0%.

The following key secondary comparison will be tested:

- Non-inferiority of switching to DTG + 3TC compared to continuation of TBR with respect to virologic success endpoint as per FDA snapshot category using a -8% non-inferiority margin.

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 Analysis

One analysis will be conducted to evaluate the primary objective of the protocol when all subjects have completed their Week 48 visit. An interim analysis will be conducted when all subjects have completed their Week 24 visit. To minimise bias, the Week 24 results will not be shared with subjects and investigators, or presented externally until after the last subject completes their last visit for the primary Week 48 analysis.

Week 96, Week 144 and Week 196 data cuts and analyses will be conducted. Further data cuts and analyses may be conducted as necessary to support regulatory submissions and publications. The Week 48 analysis will be primary. No adjustment for multiplicity will be made as the Week 24 analyses will be secondary, and other analyses are secondary/exploratory and will occur after the primary endpoint analysis at Week 48.

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 the study. An ad-hoc review of data by the IDMC will be triggered whenever the number of CVWs in the DTG + 3TC arm exceeds thresholds pre-specified in the IDMC charter. Full details of the methods, timing, decision criteria and operating characteristics will be pre-specified in the IDMC Charter.

9.4. Key Elements of Analysis Plan

The study design is open-label. However the central ViiV/GSK team responsible for the conduct and analysis of the study will not review any summaries of data grouped by treatment prior to database freeze for the Week 24 analysis.

9.4.1. Efficacy Analyses

For the primary comparison, adjusted estimates of the difference in the rate of virologic failures 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, three strata (subgroups) will be formed according to the combinations of levels of the following categorical variables:

- Baseline third agent: PI
- Baseline third agent: INI
- Baseline third agent: NNRTI

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 +3TC treated subjects, m_k is the number of INI-, NNTRI-, or PI-based ART 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.

Further efficacy analyses to assess the sensitivity of the primary endpoint will be performed and will be included in the RAP.

Changes from baseline in CD4+ lymphocyte count and in CD4+/CD8+ lymphocyte counts ratio and resistance data will be summarized. 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 using the Snapshot algorithm and changes from baseline in CD4+ lymphocyte count will be summarized by subgroups (e.g., age, gender, race).

Data gathered after subjects withdraw from IP 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, unless otherwise stated. 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 summarized 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
- Incidence of SAEs

The incidence and severity of treatment related AEs and AEs leading to withdrawal will also be assessed by baseline third agent class.

Statistical analysis of selected biomarkers and fasting lipids may be performed overall and by subgroup. Change from baseline in renal, inflammation and bone biomarkers will be summarized by treatment and visit. Change from baseline in Telomerase function will be summarized by treatment and visit. Further details will be detailed in the RAP.

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

9.4.3. Health Outcome Analyses

The reasons for Willingness to Switch at Day 1 and the change from Baseline in health related quality of life (using EQ-5D-5L) will be summarised as detailed in Section 7.7. Details of the analyses to be performed will be specified in the RAP.

9.4.4. Viral genotyping/phenotyping Analyses

The incidence of observed genotypic and phenotypic resistance to DTG, 3TC and other on-study ART will be summarized by treatment arm for subjects meeting confirmed virologic withdrawal criteria. Details of the analyses to be performed will be specified in the RAP.

9.4.5. Pharmacokinetic Analysis

See Section 11 for details.

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/GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with 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/GSK policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (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/GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

10.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and ViiV/GSK procedures, GSK monitors, or any third parties conducting the study on behalf of ViiV/GSK, 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/GSK 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.

ViiV/GSK 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, GSK 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 GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and ViiV/GSK Standard Operating Procedures.
- ViiV/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 multicenter studies, this can occur at one or more or at all sites.
- If ViiV/GSK determines such action is needed, ViiV/GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, ViiV/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/GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. ViiV/GSK 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/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, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor.
- The investigator must notify ViiV/GSK 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

No summaries of the study data according to actual randomized treatment groups will be available to sponsor staff prior to the planned Week 24 preliminary analysis. Public presentation of the Week 24 analysis will not be done prior to last subject's week 48 visit.

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/GSK site or other mutually-agreeable location.

ViiV/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.

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/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 the study. The schedule of any planned interim analysis and the analysis plan for IDMC review is described in the charter, which is available upon request. Communications received from the IDMC regarding the status of the study will be shared with investigators in a timely manner.

11. PHARMACOKINETIC SUBSTUDY

11.1. Rationale for Pharmacokinetic Evaluation

Preliminary results of the pivotal bioequivalence study (204994) showed that when administered in the fasted state, the bilayer tablet demonstrated bioequivalence to the single entity tablets for dolutegravir AUC(0-∞) & Cmax and lamivudine AUC(0-∞). However, the bilayer tablet showed a modest increase in lamivudine Cmax compared to the single entity tablet, which is not considered to be clinically significant. PK of the FDC components will be evaluated using a combination of intensive and sparse sampling.

11.1.1. Exploratory Objectives

- To assess the steady-state DTG and 3TC exposure in HIV-1 infected patients.
- To characterize the DTG and 3TC steady-state PK of the DTG/3TC FDC in HIV-1 infected patients.

11.1.2. Exploratory Endpoints

- Steady state plasma PK parameters of DTG and 3TC will be assessed using intensive PK collected at week 4.
- Population estimates of PK parameters (e.g. apparent clearance [CL/F], apparent volume of distribution [V/F]) using DTG and 3TC intensive and sparse plasma concentrations at Weeks, 4, 8, 12, 24, 36 and 48.

11.1.3. Pharmacokinetic Sample Collection

For each timepoint two separate blood samples will be collected into di-potassium ethylenediaminetetraacetic acid (K2EDTA) tubes. Table 3 and Table 4 list the sampling schedule to be followed for the assessment of intensive and sparse PK, respectively. The sub-set of subjects undergoing intensive PK sampling at selected sites will not undergo Sparse PK sampling at Week4, however, these subjects will undergo Sparse PK sampling at other PK visits (Table 3 and Table 4).

Table 3 Intensive Pharmacokinetic Sampling Schedule in a Subset of Subjects

Study visit	Sample Times Relative to Dose
Week 4	Pre-dose[a], 0.5, 1, 1.5, 2, 3, 4, 6, 10 and 24[b] hours post-dose

a. Pre-dose samples will be collected 20-28 hours after the prior dose AND approximately 15 minutes before the morning dose which will be taken under observation at the clinic.
b. Subjects in the intensive PK sampling group must return to the site the next morning immediately following the Week 4 visit for the 24 hour post-dose blood sample collection.

Table 4 Sparse Pharmacokinetic Sampling Schedule

Study Visit	PK sample collection time relative to dose	PK Sampling Group
Week 4	1 pre-dose[a,b] sample AND 1 sample 1 hour post-dose[b]	All subjects[e] except for subjects participating in the intensive PK group
Week 8	1 sample 1 to 4 hours post-dose[c]	All subjects[e]
Week 12	1 sample 4 to 12 hours post-dose[d]	
Weeks 24, 36 and 48	1 pre-dose sample[a]	

a. Pre-dose samples will be collected 20-28 hours after the prior dose AND approximately 15 minutes before the morning dose which will be taken under observation at the clinic.
b. Both sample timepoints must be obtained from each subject
c. The 1 to 4 hours sample may be drawn any time between 1 – 4 hours post-dose
d. The 4 to 12 hours sample may be drawn any time between 4 – 12 hours post-dose
e. All subjects are expected to participate in sparse PK

To allow flexibility in scheduling PK draws while maintaining quality and accuracy, the week 8 and week 12 samples can be drawn interchangeably (i.e. 1 to 4 hours post-dose drawn at week 12 and the 4 to 12 hours post-dose drawn at week 8) as long as both the 1 to 4 hours post-dose and 4 to 12 hours post-dose samples are obtained for each subject. In addition, flexibility is allowed in collecting the post-dose sample anywhere from 1 to 4 hours and 4 to 12 hours so that a range of sample time can be obtained. To achieve this, the subject may choose to remain in clinic until at least 1 hour after taking the DTG dose and may choose to return to the clinic 4 to 12 hours after taking the medication.

It is important to collect PK samples according to the following procedures:

- To enhance the quality of the data, subjects undergoing intensive and/or sparse PK assessments will be asked to complete a diary card with the following information which will be included in eCRF:
    - The date and time of the DTG/3TC FDC administration for 3 days prior to the scheduled PK clinic visit;
    - Whether or not the doses were taken with a meal
    - Whether or not the subject vomited within 4 hours of taking the study drug

In addition the following information should be recorded in the eCRF:

- The actual date and time of the observed dose taken at the clinic visit;
- The actual date and time of the PK samples collected

- For the 3 days in advance of a PK clinic visit, the subject must be instructed to take the DTG/3TC FDC without regard to food at a time that corresponds with the

scheduled PK visit time to allow for a pre-dose sample collection as close to 24 hour after the previous dose.

- On the days of the either intensive PK or sparse pre-dose sample collection, the subjects should not take a dose of the DTG/3TC FDC until instructed at the clinic visit.

- The subjects participating in **intensive PK sampling** will be requested to present at the clinic fasted for at least 8 hours at the week 4 visit. These subjects should return to the clinic next day for the 24 hours post-dose sample collection, prior to taking a DTG/3TC FDC dose. The 24 hours post-dose sample may be collected without regard to food.

- The sparse PK samples will be collected without regard to food (however the fed/fasted status information will be collected and recorded on the eCRF)

Note: If a subject presents at the clinic for pre-dose PK sample collection having already taken the daily dose or having missed doses within the previous 3 days, it is recommended to reschedule PK sampling as early as possible within the defined PK visit window. It is recommended not to collect PK samples if date and time of dosing for the previous 3 days cannot reliably be confirmed. If PK cannot be rescheduled within the pre-defined visit of interest window (specified in the study procedure manual), no PK sample is to be collected for that visit.

11.1.4. Bioanalysis of DTG and 3TC Samples

The bioanalysis of plasma DTG and 3TC samples will be performed by PPD using GSK validated LC/MS/MS assay.

11.1.5. Pharmacokinetic Populations

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

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

The defining of evaluable drug concentrations and further details on the PK populations will be described in the RAP.

11.1.6. Pharmacokinetic Analyses

The following intensive PK parameters will be summarized for 3TC and DTG: maximum observed plasma concentration (Cmax); time to maximum observed plasma concentration (tmax); observed plasma concentration at the end of a dosing interval (Ctau); observed pre-dose plasma concentration (C0); area under the concentration-time curve in one dosing interval (AUC(0-τ)).

11.1.7. Population PK

If data permits, the sparse PK data will be pooled with the intensive PK data and potentially data from other studies to perform integrated PK analyses for DTG and 3TC to estimate steady-state AUC, Cmax and Cτ for individual subjects. Further details of the PK analyses will be provided in the RAP. The population PK analyses may be reported separately.

12. REFERENCES

Arribas JR, Girard PM, Landman R, et. al. Dual treatment with lopinavir-ritonavir plus lamivudine versus triple treatment with lopinavir-ritonavir plus lamivudine or emtricitabine and a second nucleos(t)ide reverse transcriptase inhibitor for maintenance of HIV-1 viral suppression (OLE): a randomised, open-label, non-inferiority trial. *Lancet Infect Dis*. 2015;15:785–92.

Arribas JR, Pialoux G, Gathe J, et. al. Simplification to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus continuation of ritonavir-boosted protease inhibitor with emtricitabine and tenofovir in adults with virologically suppressed HIV (STRATEGY-PI): 48 week results of a randomised, open-label, phase 3b, non-inferiority trial. *Lancet Infect Dis*. 2014;14:581–89.

British HIV Association (BHIVA) guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015 (2016 interim update). Available at: http://www.bhiva.org/documents/Guidelines/Treatment/2016/treatment-guidelines-2016-interim-update.pdf. Accessed February 8, 2017.

Cahn P, Madero JS, Arribas J, et al. Non-inferior efficacy of dolutegravir (DTG) plus lamivudine (3TC) versus DTG plus tenofovir/emtricitabine (TDF/FTC) fixed-dose combination in antiretroviral treatment-naive adults with HIV-1 infection: 48-week results from the GEMINI studies. AIDS 2018: 22nd International AIDS Conference, Amsterdam, Netherlands, July 23-27, 2018. Abstract TUAB0106LB. http://programme.aids2018.org/Abstract/Abstract/13210.

Carr A, Hoy J, Pozniak A (2012). The Ethics of Switch/Simplify in ART Trials: Non-Inferior or Just Inferior? PLoS Med 9(7): e1001240. doi:10.1371/journal.pmed.1001240. Available at: http://journals.plos.org/plosmedicine/article/asset?id=info:doi/10.1371/journal.pmed.1001240.PDF. Accessed April 19, 2016.

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

Clotet B, Feinberg J, van Lunzen J, et al. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naïve adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. *Lancet*. 2014;383:2222-31.

Department of Health and Human Services (DHHS). Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. July 2016. Available at: https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0. Accessed February 8, 2017.

Descovy Product Insert. Available at: http://www.gilead.com/~/media/files/pdfs/medicines/hiv/descovy/descovy_pi.pdf?la=en. April 2016. Accessed February 8, 2017.

Dolutegravir (Tivicay) Product Information. November 2017.

Epivir (Lamivudine) Product Information. September 2017.

Eron JJ, Benoit SL, Jemsek J, et. al. Treatment with Lamivudine, Zidovudine, or both in HIV-Positive Patients with 200 to 500 CD4+ Cells per Cubic Millimeter. *N Engl J Med*. 1995;333:1662-69.

European AIDS Clinical Society (EACS) Guidelines for the clinical management and treatment of HIV Infected Adults in Europe. Version 8.0, October 2015. Available at: http://www.eacsociety.org/files/2015_eacsguidelines_8_0-english_rev-20160124.pdf. Accessed February 8, 2017.

FleissJL. Statistical Methods for Rates and Proportions. 2nd ed. New York:John Wiley; 1981.

Gallant, JE, Daar ES, Raffi F, et. al. Efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate given as fixed-dose combinations containing emtricitabine as backbones for treatment of HIV-1 infection in virologically suppressed adults: a randomised, double-blind, active-controlled phase 3 trial. *Lancet HIV*. 2016;3:e158–65.

Genvoya Package Insert. Available at: http://www.gilead.com/~/media/files/pdfs/medicines/hiv/genvoya/genvoya_pi.pdf. December 2016. Accessed February 8, 2017.

GlaxoSmithKline (GSK) Document Number RM2007/00683/11: Clinical Investigator's Brochure for GSK1349572 (Dolutegravir) Version 11. October 2017.

GlaxoSmithKline Document Number 2017N352880_00: GSK1349572 Clinical Investigator's Brochure, Version 11, Supplement 01, 11 December 2017.

GlaxoSmithKline Document Number 2017N352880_01: GSK1349572 Clinical Investigator's Brochure, Version 11, Supplement 02, June 2018.

Gunthard HF, Saag MS, Benson CA, et. al. Antiretroviral drugs for the treatment and prevention of HIV infection in adults. 2016 recommendations of the International Antiviral Society (IAS)-USA Panel. *JAMA*. 2016;316(2):191-210.

Herdman M, Gudex C, Lloyd A, et. al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res.* 2011;20:1727-36.

Kuritzkes DR, Quinn JB, Benoit SL, et. al. Drug resistance and virologic response in NUCA 3001, a randomized trial of lamivudine (3TC) versus zidovudine (ZDV) versus ZDV plus 3TC in previously untreated patients. *AIDS*. 1996;10:975–81.

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.

Levey AS, Stevens LA, Schmid CH, et.al. A new equation to estimate glomerular filtration rate. *Ann Int Med*. 2009;150:604-12.

Libre JM, Hung C-C, Brinson C, et. al. Phase III SWORD 1&2: Switch to DTG+RPV maintains virologic suppression through 48 wks. 2017 CROI, Seattle. Abstract 44LB.

Lui KJ, Kelly C. A revisit on tests for the homogeneity of the risk difference. Biometrics. 2000;56:309-15.

Margolis DA, Brinson CC, Smith GH, et. al. Cabotegravir plus rilpivirine, once a day, after induction with cabotegravir plus nucleoside reverse transcriptase inhibitors in antiretroviral-naïve adults with HIV-1 infection (LATTE): a randomised, phase 2b, dose-ranging trial. *Lancet Infect Dis*. 2015 Oct; 15(10):1145-55. doi: 10.1016/S1473-3099(15)00152-8.

Mills A , Arribas JR, Andrade-Villanueva J, et. al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in antiretroviral regimens for virologically suppressed adults with HIV-1 infection: a randomised, active-controlled, multicentre, open-label, phase 3, non-inferiority study. *Lancet Infect Dis*. 2016;16:43–52.

Odefsey Product Insert. Available at: http://www.gilead.com/~/media/files/pdfs/medicines/hiv/odefsey/odefsey_pi.pdf?la=en. March 2016. Accessed February 8, 2017.

Palella FJ, Fisher M, Tebas P, et. al. Simplification to rilpivirine/emtricitabine/tenofovir disoproxil fumarate from ritonavir-boosted protease inhibitor antiretroviral therapy in a randomized trial of HIV-1 RNA-suppressed participants. *AIDS.* 2014;28:335-44.

Perez-Molina. Dual treatment with atazanavir–ritonavir plus lamivudine versus triple treatment with atazanavir–ritonavir plus two nucleos(t)ides. *Lancet Infect Dis.* 2015;15:775–84.

Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *Am J Psychiatry*. 2007;164:1035–43.

Pozniak A, Markowitz M, Mills A, et. al. Switching to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus continuation of non-nucleoside reverse transcriptase inhibitor with emtricitabine and tenofovir in virologically suppressed adults with HIV (STRATEGY-NNRTI): 48 week results of a randomised, open-label, phase 3b non-inferiority trial. *Lancet Infect Dis*. 2014;14:590-99.

Raffi F, Rachlis A, Stellbrink H-J, et. al. Once-daily dolutegravir is non-inferior to raltegravir in ART naive adults with HIV-1 infection: 48 week results from the randomized, double-blind study SPRING-2. *Lancet*. 2013;381:735–43.

Sato T. On the variance estimator for the Mantel-Haenszel risk difference. Biometrics.1989;45:1323-24.

Solomon A, Tennakoon S, Leeansyah E, et al. (2014) No Difference in the Rate of Change in Telomere Length or Telomerase Activity in HIV-Infected Patients after Three

Years of Darunavir/Ritonavir with and without Nucleoside Analogues in the MONET Trial. PLoS ONE 9(11): e109718. doi:10.1371/journal.pone.0109718. Available at: http://journals.plos.org/plosone/article/asset?id=10.1371/journal.pone.0109718.PDF. Accessed February 8, 2017.

Stella-Ascariz N, Montejano R, Pintado-Berninches P, et al. Brief Report: Differential effects of tenofovir, abacavir, emtricitabine, and darunavir on telomerase activity in vitro. *J. Acquir Immune Defic Syndr* 2017;74:91-94.

Trottier B, Lake J, Logue K, et. al. Switching to Abacavir/Dolutegravir/Lamivudine Fixed Dose Combination (ABC/DTG/3TC FDC) from a PI, INI or NNRTI Based Regimen Maintains HIV Suppression. ICAAC/ICC 2015, San Diego, CA, USA, Sep 17-21, 2015. 2015-LB-3271-ASM-ICAAC.

U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for Industry: Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment. November 2015 Available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm355128.pdf. Accessed February 8, 2017

Walmsley SL, Antela A, Clumeck N, et. al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. *N Engl J Med.* 2013;369(19):1807-18.

Wensing AM, Calvez V, Günthard HF, et. al. IAS-USA. Topics in Antiviral Medicine. Special Contribution. Update of the drug resistance mutations in HIV-1. 2017 Drug Resistance Mutations Update. 2017; 24(4):132-41. December 2016/January 2017.

13. APPENDICES

13.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

3TC	Lamivudine, EPIVIR
ABC	Abacavir, ZIAGEN
ABC/3TC	Abacavir/lamivudine, EPZICOM, KIVEXA
ADR	Adverse drug reaction
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
Anti-HBc	Hepatitis B core Antibody
ARV	Antiretroviral
ART	Antiretroviral therapy
ATV	Atazanavir
ATV/r	Atazanavir/ritonavir
AST	Aspartate aminotransferase
AUC (0-∞)	Area under the curve zero to infinity
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
c/mL	Copies/milliliter
CAR	Current ART regimen
cART	Combination ART
CDC	Centers for Disease Control and Prevention
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cmax	Maximum concentration
CMH	Cochran-Mantel Haenszel
CRF	Case Report Form
CSR	Clinical Study Report
C-SSRS	Columbia Suicidality Severity Rating Scale
CI	Confidence interval
COBI	Cobicistat
ConART	Concomitant ART therapy
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CV	Cardiovascular
CVW	Confirmed Virologic Withdrawal
DAIDS	Division of Acquired Immunodeficiency Syndrome
DDI	Drug Drug Interaction
DILI	Drug induced liver injury
DNA	Deoxyribonucleic acid
DP	Diphosphate
DRV	Darunavir
DTG	Dolutegravir, TIVICAY

E/C/F/TAF	Elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide
E/C/F/TDF	Elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate
ECG	Electrocardiogram
eCRF	Electronic case report form
eC-SSRS	Electronic Columbia Suicidality Severity Rating Scale
eDM	Electronic Data Management
EFV	Efavirenz
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EQ-5D-5L	European Quality of Life-5 Dimensions-5 Levels
ETR	Etravirine
EU	European Union
EVG	Elvitegravir
FDA	Food and Drug Administration
FDC	Fixed-dose combination
FSFV	First subject first visit
FTC	Emtricitabine
GCP	Good Clinical Practice
GCSP	GSK's Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
GFR	Glomerular Filtration rate
HAART	Highly active ART therapy
HbA1c	Glycated henoglobin
HBsAb	Hepatitis B surface Antibody
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High density lipoprotein
HDPE	High density polyethylene
HIV	Human immunodeficiency virus
HIV TSQ	HIV treatment satisfaction questionnaire
HLA	Human leukocyte antigen
HOMA-IR	Homeostasis model of assessment-insulin resistance
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
INI	Integrase inhibitor
INSTI	Integrase strand transfer inhibitor
INR	International normalized ratio
IP	Investigational Product
IRB	Institutional Review Board

ITT-E	Intent-to-treat exposed
IUD	Intrauterine device
IRT	Interactive response technology
IVRS/IWRS	Interactive Voice/Web Recognition System
LDL	Low density lipoprotein
LOCF	Last Observation Carried Forward
Lp-PLA2	Lipoprotein-associated phospholipase A2
LPV	Lopinavir
MCH	Mean Corpuscular Hemoglobin
MCv	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
Mg	Milligram
Mg/dL	Milligram per deciliter
m-ITT	Modified Intent to Treat
MSD=F	Missing, switch, or discontinuation equals failure
MSDS	Material Safety Data Sheet
NADES	Non-Acquired Immuno-Deficiency Syndrome (AIDS)-Defining Events
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
OC	Observed Case
OCT-2	Organic cation transporter
PBMC	Peripheral Blood Mononuclear Cell
PDVF	Protocol defined virologic failure
PI	Protease inhibitor
PK	Pharmacokinetic
PP	Per-protocol
PPD	Pharmaceutical Product Development
PRO	Protease
PRTD	Proximal Renal Tubule Dysfunction
PSRAE	Possible suicidality-related adverse event
QTc	Corrected QT interval
RAL	Raltegravir
RAP	Reporting and Analysis Plan
RBC	Red blood cell
RNA	Ribonucleic acid
RPV	Rilpivirine, Edurant
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
TAF	Tenofovir alafenamide
TBR	TAF based regimen

TDF/FTC	Tenofovir disoproxil fumarate/Emtricitabine, Truvada
TEN	Toxic epidermal necrolysis
TLOVR	Time To Loss Of Virologic Response
TSQ	Treatment Satisfaction Questionnaire
TRDF	Treatment Related Discontinuation = Failure
ULN	Upper limit of normal
VAS	Visual Analog Scale
US	United States
VSLC	ViiV Safety and Labelling Committee
WBC	White blood cell

Trademark Information

Trademarks of ViiV Healthcare
EPIVIR
EPZICOM/KIVEXA
TIVICAY
TRIUMEQ
ZIAGEN

Trademarks not owned by ViiV Healthcare
Abbot Realtime HIV-1
Descovy
Edurant
EQ-5D-5L
GenoSure
Genvoya
Monogram Biosciences
Odefsey
PhenoSense
SAS
Truvada

13.2. Appendix 2: 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 13.9). Additional information regarding detecting, documenting and reporting AEs and SAEs are available in Section 7.4.

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

No toxicity-related dose reductions of study drugs will be allowed. Study drugs should be restarted as soon as medically appropriate; in general, this should be no longer than 4 weeks after interruption (unless Grade 3 or 4 toxicities persist). Decisions regarding sequential reintroduction of study drugs or temporary interruption of one but not all drugs within the ART regimen should be made with the understanding that these changes may result in incomplete viral suppression and selection of resistant virus. Guidance is provided below on 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 13.2.1.7 and rash in Section 13.2.1.6.

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 13.2.1.7. 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.

13.2.1. 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 (see Section 5.4).

13.2.1.1. 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 Section 5.4.

13.2.1.2. Restarting Study Drug

Refer to Section 13.6 for details on drug restart following transient resolving liver events not related to study treatment.

13.2.1.3. Decline in Renal Function

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

Subjects who experience progression to an estimated GFR (using the CKD-EPI-creatinine) of < 30 mL/min/1.73m^2 must return for a confirmatory assessment within 2 weeks [Levey, 2009]. A urinalysis, urine albumin/creatinine and urine protein/creatinine ratios, serum cystatin C and an estimated GFR using the CKD-EPI (cystatin C) [Inker, 2012] should be done at this confirmatory visit. If an estimated GFR of < 30 mL/min/1.73m^2 is confirmed using the CKD-EPI (cystatin C), 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 a study of a fixed-dose combination tablet).

13.2.1.4. 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 and protein/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.

13.2.1.5. 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, 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.

13.2.1.6. 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 most current version of the DTG IB and any IB supplements [GSK Document Number RM2007/00683/11, GSK Document Number 2017N352880_00, GSK Document Number 2017N352880_01].

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, Section 13.9.

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.

13.2.1.7. 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.

13.2.1.8. 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.

REFERENCE:

Inker LA, Schmid CH, Tighiouart H, et al; Estimating Glomerular Filtration Rate from Serum Creatinine and Cystatin C. *N Engl J Med*. 2012;367:20-9.

Levey AS, Stevens LA, Schmid CH, et.al. A new equation to estimate glomerular filtration rate. *Ann Int Med*. 2009;150:604-12.

13.3. Appendix 3: Pregnancy Information

13.3.1. Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) and Collection of Pregnancy Information

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.

- Contraceptive subdermal implant
- Intrauterine device or intrauterine system
- Combined estrogen and progestogen oral contraceptive [Hatcher, 2011]
- Injectable progestogen [Hatcher, 2011]
- Contraceptive vaginal ring [Hatcher, 2011]
- Percutaneous contraceptive patches [Hatcher, 2011]
- 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.

13.3.2. 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/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/GSK/PPD. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. GSK's central safety department also will forward this information to the Antiretroviral Pregnancy Registry. The international registry is jointly sponsored by manufacturers or licensees of antiretroviral products. Additional information and a list of participating manufacturers/licensees are available from http://www.apregistry.com/.
- Any termination of pregnancy will be reported, regardless of 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 for medical reasons 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 Section 13.8. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female 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.

13.4. Appendix 4: 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 5). For subjects requiring anticoagulation therapy, discussion with the study medical monitor will be required.

Table 5 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/behavior, decerebrate, slow 2-3 cycles per second delta activity
[Pugh, 1973; Lucey, 1997]

References

Lucey MR, Brown KA, Everson GT, et al. Minimal criteria for placement of adults on the liver transplant waiting list: a report of a national conference organized by the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases. *Liver Transpl Surg*. 1997;3:628-37.

Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg*. 1973;60:646-49.

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

Table 6 Liver Chemistry Stopping Criteria: Required Actions and Follow up Assessments

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 is > 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]
• Perform liver event follow up assessments
• Complete the liver imaging and/or liver biopsy eCRFs if these tests are performed
• Monitor the subject until liver chemistries resolve , stabilize, or return to within baseline (see **MONITORING** below)
• **Do not restart** subject with study treatment unless allowed per protocol and ViiV Safety and Labelling Committee approval **is granted** (refer to **Appendix 6**)
• If restart **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[4]
	• 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 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

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, stabilize or return to within baseline • A specialist or hepatology consultation is recommended	within 60 hours after last dose[4] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin ≥2xULN • Obtain complete blood count with differential to assess eosinophilia • 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 case report form

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that 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) or ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to 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. PK sample may not be required for subjects known to be receiving placebo or non- ViiV/GSK standard-of-care treatments. 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.

References

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; 37:1779-84.

Table 7 Liver Chemistry Increased Monitoring Criteria With Continued Therapy

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 they resolution or stabilisation (ALT < 5xULN on 2 consecutive evaluations) If at any time subject meets the liver chemistry stopping criteria, proceed as described above

13.6. Appendix 6: 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 8, Figure 4).

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 4)

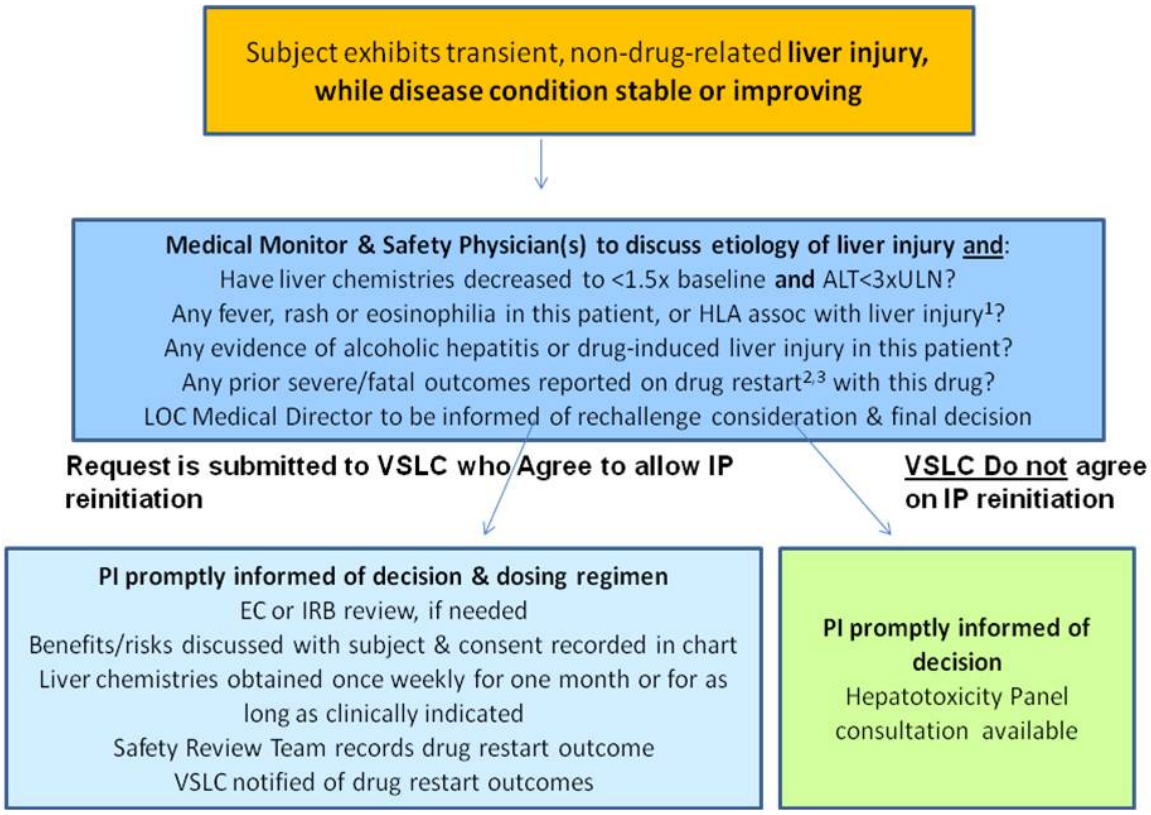
- PI requests consideration of drug re-initiation for a subject stable or improving on study drug, who exhibits liver chemistry elevation meeting subject stopping criteria, which is transient, non-drug-related, and liver chemistries improve to within 1.5x baseline and ALT< 3xULN.
- Medical monitor and Clinical Safety Physician to review the subject's diagnosis, restart risk factors and complete checklist (Table 8).
- 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 8 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 4 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.

13.7. Appendix 7: 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.

13.8. Appendix 8: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

13.8.1. 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 unfavorable 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 (hematology, 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.

13.8.2. 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., hospitalization 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 hospitalization or prolongation of existing hospitalization

NOTE:

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

d) Results in 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, diarrhea, 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 hospitalization but may jeopardize 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 hospitalization, or development of drug dependency or drug abuse

g) Is associated with liver injury and impaired liver function defined as:

- ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or**
- ALT ≥ 3xULN and INR** > 1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

13.8.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:

- 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
- Revascularization

13.8.4. Sentinel Events

Sentinel Event Definition:

A sentinel event is a ViiV/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 ViiV/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 ViiV/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)

13.8.5. 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 ViiV/GSK in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by ViiV/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 to ViiV/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.

13.8.6. 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 Section 13.9:

- 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 Investigator Brochure (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 ViiV/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/GSK.**
- 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 ViiV/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 recognized follow-up period, the investigator will provide ViiV/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/GSK within the designated reporting time frames.

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

Reporting of SAEs and other events to ViiV/GSK/PPD
• Primary mechanism for reporting SAEs to ViiV/GSK/PPD 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 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 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.

13.9. Appendix 9: Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.1, March 2017

VERSION 2.1, March 2017

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE Grading Table") is a descriptive terminology which can be 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 +5mmHg 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	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)

[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

Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hemorrhage (with significant acute blood loss)	NA	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤ 2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children, packed RBCs > 10 cc/kg) indicated
Prolonged PR Interval or AV Block *Report only one* *> 16 years of age*	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
≤ 16 years of age	1st degree AV block (PR interval > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
Prolonged QTc Interval[2]	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds OR ≥ 0.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism *Report only one*	NA	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)

[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 area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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 (page 23 in source DAIDS Table).

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy[4]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA
Lipohypertrophy[5]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

[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 consequences
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 indicatedP	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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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
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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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
Stillbirth (report using mother's participant ID) *Report only one*	NA	NA	Fetal death occurring at ≥ 20 weeks gestation	NA
Preterm Birth (report using mother's participant ID)	Live birth at 34 to < 37 weeks gestational age	Live birth at 28 to < 34 weeks gestational age	Live birth at 24 to < 28 weeks gestational age	Live birth at < 24 weeks gestational age

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Spontaneous Abortion or Miscarriage[7] (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 pregnancy loss 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 causing no or minimal interference with usual social & functional activities	Moderate difficulty falling asleep, staying asleep, or waking up early causing more than minimal interference with usual social & functional activities	Severe difficulty falling asleep, staying asleep, or waking up early causing inability to perform usual social & functional activities requiring intervention or hospitalization	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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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 Medical 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[8]	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[9] (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[10]	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[11] *> 5 to 19 years of age*	WHO BMI z-score < -1 to -2	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	WHO BMI z-score < -1 to -2	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	WHO BMI z-score < -1 to -2	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
Unintentional 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)

[8] Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.

[9] For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23 in source DAIDS Table).

[10] Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea

[11] WHO reference tables may be accessed 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[12] *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

[12] 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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
AST or SGOT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to < LLN *16.0 to < LLN*	11.0 to < 16.0 *11.0 to < 16.0*	8.0 to < 11.0 *8.0 to < 11.0*	< 8.0 *< 8.0*
Bilirubin ***Direct Bilirubin[13], High*** *> 28 days of age*	NA	NA	> ULN with other signs and symptoms of hepatotoxicity.	> 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 with other signs and symptoms of hepatotoxicity.	≥ 5.0 x ULN with life-threatening consequences (e.g., signs and symptoms of liver failure).
≤ 28 days of age	See Appendix A in Source DAIDS Table. Total Bilirubin for Term and Preterm Neonates	See Appendix A in Source DAIDS Table. Total Bilirubin for Term and Preterm Neonates	See Appendix A in Source DAIDS Table. Total Bilirubin for Term and Preterm Neonates	See Appendix A in Source DAIDS Table. 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*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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
Creatine Kinase, High	3 to < 6 x ULN	6 to < 10x ULN	10 to < 20 x ULN	≥ 20 x ULN
Creatinine, High **Report only one*	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase to 1.3 to < 1.5 x participant's baseline	> 1.8 to < 3.5 x ULN OR Increase to 1.5 to < 2.0 x participant's baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x participant's baseline
Creatinine Clearance[14] 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 participant's baseline	< 60 to 30 ml/min or ml/min/1.73 m^2 OR 30 to < 50% decrease from participant's baseline	< 30 ml/min or ml/min/1.73 m^2 OR ≥ 50% decrease from participant's 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*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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 *≥ 18 years of age*	130 to < 160 *3.37 to < 4.12*	160 to < 190 *4.12 to < 4.90*	≥ 190 *≥ 4.90*	NA
> 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[15], 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 *0.65 to < LLN*	1.4 to < 2.0 *0.45 to < 0.65*	1.0 to < 1.4 *0.32 to < 0.45*	< 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*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
< 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 < 130*	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*

*Reminder: An asymptomatic abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited time frame unless it meets protocol-specific reporting requirements.

[13] 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

[14] Use the applicable formula (i.e., Cockcroft-Gault in mL/min or Schwartz, MDRD, CKD-Epi in mL/min/1.73m2). Sites should choose the method defined in their study and when not specified, use the method most relevant to the study population.

*Reminder: Choose the method that selects for the higher grade

[15] To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114

Hematology

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*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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_9} *to* *< 0.600 x* 10^9	350 to < 500 *0350 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 age*	800 to 1,000 *0.800 x* 10^9 *to 1.000 x* 10^9	600 to 799 *0.600 x* 10^9 *to 0.799 x* 10^9	400 to 599 *0.400 x* 10^9 *to 0.599 x* 10^9	< 400 *< 0.400 x* 10^9
2 to 7 days of age	1,250 to 1,500 *1.250 x* 10^9 *to 1.500 x* 10^9	1,000 to 1,249 *1.000 x* 10^9 *to 1.249 x* 10^9	750 to 999 *0.750 x* 10^9 *to 0.999 x* 10^9	< 750 *< 0.750 x* 10^9
≤ 1 day of age	4,000 to 5,000 *4.000 x* 10^9 *to 5.000 x* 10^9	3,000 to 3,999 *3.000 x* 10^9 *to 3.999 x* 10^9	1,500 to 2,999 *1.500 x* 10^9 *to 2.999 x* 10^9	< 1,500 *< 1.500 x* 10^9
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to < 200 *1.00 to < 2.00* OR 0.75 to < 1.00 x LLN	75 to < 100 *0.75 to < 1.00* OR ≥ 0.50 to < 0.75 x LLN	50 to < 75 *0.50 to < 0.75* OR 0.25 to < 0.50 x LLN	< 50 *< 0.50* OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin[16], Low (g/dL; *mmol/L*)[17] *≥ 13 years of age (male only)*	10.0 to 10.9 *6.19 to 6.76*	9.0 to < 10.0 *5.57 to < 6.19*	7.0 to < 9.0 *4.34 to < 5.57*	< 7.0 *< 4.34*
≥ 13 years of age (female only)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
57 days of age to < 13 years of age (male and female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
36 to 56 days of age (male and female)	8.5 to 9.6 *5.26 to 5.99*	7.0 to < 8.5 *4.32 to < 5.26*	6.0 to < 7.0 *3.72 to < 4.32*	< 6.0 *< 3.72*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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 therapy)	1.1 to < 1.66 x ULN	1.66 to < 2.33 x ULN	2.33 to < 3.00 x ULN	≥ 3.00 x ULN
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to < 125,000 *100.000 x 10^9 to < 125.000 x 10^9*	50,000 to < 100,000 *50.000 x 10^9 to < 100.000 x 10^9*	25,000 to < 50,000 *25.000 x 10^9 to < 50.000 x 10^9*	< 25,000 *< 25.000 x 10^9*
PT, High (not on anticoagulation therapy	1.1 to < 1.25 x ULN	1.25 to < 1.50 x ULN	1.50 to < 3.00 x ULN	≥ 3.00 x ULN
WBC, Decreased (cells/mm^3; *cells/L*) *> 7 days of age*	2,000 to 2,499 *2.000 x 10^9 to 2.499 x 10^9*	1,500 to 1,999 *1.500 x 10^9 to 1.999 x 10^9*	1,000 to 1,499 *1.000 x 10^9 to 1.499 x 10^9*	< 1,000 *< 1.000 x 10^9*
≤ 7 days of age	5,500 to 6,999 *5.500 x 10^9 to 6.999 x 10^9*	4,000 to 5,499 *4.000 x 10^9 to 5.499 x 10^9*	2,500 to 3,999 *2.500 x 10^9 to 3.999 x 10^9*	< 2,500 *< 2.500 x 10^9*

[16] Male and female sex are defined as sex at birth. For transgender participants ≥ 13 years of age who have been on hormone therapy for more than 6 consecutive months grade hemoglobin based on the gender with which they identify (i.e., a transgender female should be graded using the femaile sex at birth hemoglobin laboratory values).

[17] The most commonly used conversion factor to convert g/dL to mmol/L is 0.6206. 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 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

Appendix A: Total Bilirubin Table for Term and Preterm Neonates

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Total Bilirubin[18], **High** (mg/dL; *µmol/L*)[19] ***Term Neonate***[20] *< 24 hours of age*	4 to < 7 *68.4 to < 119.7*	7 to < 10 *119.7 to < 171*	10 to < 17 *171 to < 290.7*	≥ 17 *≥ 290.7*
24 to < 48 hours of age	5 to < 8 *85.5 to < 136.8*	8 to < 12 *136.8 to < 205.2*	12 to < 19 *205.2 to < 324.9*	≥ 19 *≥ 324.9*
48 to < 72 hours of age	8.5 to < 13 *145.35 to < 222.3*	13 to < 15 *222.3 to < 256.5*	15 to < 22 *256.5 to < 376.2*	≥ 22 *≥ 376.2*
72 hours to < 7 days of age	11 to < 16 *188.1 to < 273.6*	16 to < 18 *273.6 to < 307.8*	18 to < 24 *307.8 to < 410.4*	≥ 24 *≥ 410.4*
7 to 28 days of age (breast feeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 *≥ 427.5*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
7 to 28 days of age (not breast feeding)	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
Preterm Neonate[20] *35 to < 37 weeks gestational age*	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).
32 to < 35 weeks gestational age and < 7 days of age	NA	NA	10 to < 14 *171 to < 239.4*	≥ 14 *≥ 239.4*
28 to < 32 weeks gestational age and < 7 days of age	NA	NA	6 to < 10 *102.6 to < 171*	≥ 10 *≥ 171*
< 28 weeks gestational age and < 7 days of age	NA	NA	5 to < 8 *85.5 to < 136.8*	≥ 8 *≥ 136.8*
7 to 28 days of age (breast feeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 *≥ 427.5*
7 to 28 days of age (not breast feeding)	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

[18] Severity grading for total bilirubin in neonates is complex because of rapidly changing total bilirubin normal ranges in the first week of life followed by the benign phenomenon of breast milk jaundice after the first week of life. Severity grading in this appendix corresponds approximately to cut-offs for indications for phototherapy at grade 3 and for exchange transfusion at grade 4.

[19] A laboratory value of 1 mg/dL is equivalent to 17.1 µmol/L.

[20] Definitions: Term is defined as ≥ 37 weeks gestational age; near-term, as ≥ 35 weeks gestational age; preterm, as < 35 weeks gestational age; and neonate, as 0 to 28 days of age.

13.10. Appendix 10: Country Specific Requirements

13.10.1. 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.

The date of last study treatment administration in the UK will be determined by the completion of the Week 200 visit for the last UK subject enrolled. The last subject was enrolled by June 2018, and hence the last study treatment administration will occur by Q3 2022. (Note: For subjects in the UK, the study and provision of IP is anticipated to conclude by Q3 2022, at which time the dual regimen of DTG plus 3TC would be available as it is anticipated to be approved in Q3/Q4 2020).

13.10.2. Japan

All drug will be provided centrally. In Japan, only subjects receiving Descovy +DTG as their TBR are eligible for the study.

13.11. Appendix 11 Protocol Changes

13.11.1. Amendment 01 (2017-MAY-16): A global amendment applicable to all participating countries

Summary of Key Changes in Protocol Amendment 01 and Rationale

- Tenofovir alafenamide (TAF) was corrected by removal of the word “fumarate”.
- Clarification was provided in the overall design to specify that subjects randomized to TBR will switch to DTG + 3TC at Week 52 if HIV-1 RNA <50 c/mL at Week 48 (or upon retest by Week 52).
- Biomarkers of inflammation and mitochondrial function were removed as exploratory endpoints.
- A Week 96 endpoint was added to the measurement of biomarkers of telomerase function in a subset of subjects.
- Cardiovascular biomarker measurements were removed as exploratory endpoints.
- Inclusion Criterion #5 was edited for clarity.
- New section added as Sec 6.2, Protocol Permitted Substitutions, clarifying a switch from a PI boosted with RTV to the same PI boosted with cobisistat is allowed, and vice versa.
- The text defining the TBR comparators as investigational medicinal product was removed; TBR comparators will be provided in designated, specific countries only, as needed.
- The Time and Events Table was modified to clarify that whole blood samples may be utilized for virology and for telomere length measurements, and cryopreserved PBMCs will be used to evaluate telomerase activity.
- Updated version of Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (v2.1), March 2017, was provided in Section 12.9.
- Changes were made to the protocol text to reflect the addition of Country Specific requirements for Japan.
- Minor revisions were made to the text to correct errors and improve accuracy.

List of Specific Changes

Section 1. Rationale (also updated in Sec. 12.1 Appendix 1 Abbreviations and Trademarks):

Previous text:

Study 204862 is being conducted to establish if human immunodeficiency virus type 1 (HIV-1) infected adult subjects with current virologic suppression on a ≥3-drug tenofovir alafenamide ~~**fumarate**~~ (TAF) based regimen (TBR) remain suppressed upon switching to a two-drug regimen of dolutegravir (DTG) 50 mg + lamivudine (3TC) 300 mg.

Current text:

Study 204862 is being conducted to establish if human immunodeficiency virus type 1 (HIV-1) infected adult subjects with current virologic suppression on a ≥3-drug tenofovir alafenamide (TAF) based regimen (TBR) remain suppressed upon switching to a two-drug regimen of dolutegravir (DTG) 50 mg + lamivudine (3TC) 300 mg.

- **Section 1. Overall Design (also updated in Section 4.1):**

Previous Text:

Approximately 766 HIV-1 infected adults who are on a stable TBR will be randomized 1:1 to switch to DTG + 3TC once daily (DTG + 3TC arm) for up to 100 weeks, or to continue their TBR for 52 weeks, at which time and if HIV1 RNA <50 c/mL at Week 48 these subjects will switch to DTG + 3TC up to Week 100.

Current Text:

Approximately 766 HIV-1 infected adults who are on a stable TBR will be randomized 1:1 to switch to DTG + 3TC once daily (DTG + 3TC arm) for up to 100 weeks, or to continue their TBR for 52 weeks, at which time and if HIV1 RNA <50 c/mL at Week 48 **(or upon re-test by Week 52),** these subjects will switch to DTG + 3TC up to Week 100.

- **Section 1. Synopsis, Overall Design:**

Deleted paragraph (this was duplicate text):

All subjects who successfully complete up to 100 weeks of treatment will have the opportunity to continue receiving these agents until either DTG + 3TC Fixed dose Combination (FDC) is locally approved and commercially available, they no longer derive clinical benefit, they meet a protocol-defined reason for discontinuation, or until development of DTG plus 3TC dual regimen is terminated.

- **Section 2.1. Study Rationale:**

Previous Text:

Compared to tenofovir disoproxil fumarate (TDF)-based regimens, tenofovir alafenamide ~~**fumarate**~~ (TAF) based regimen (TBRs) are associated with short-term improvements in renal and bone biomarkers in both treatment-naive and treatment-experienced persons [Genvoya, 2016].

Current Text:

Compared to tenofovir disoproxil fumarate (TDF)-based regimens, tenofovir alafenamide (TAF) based regimens (TBRs) are associated with short-term improvements in renal and bone biomarkers in both treatment-naive and treatment-experienced persons [Genvoya, 2016].

- **Section 3. Objectives and Endpoints:**

Previous Text:

To evaluate biomarkers of ~~inflammation, mitochondrial function and~~ telomerase ~~activity~~ in a subset of subjects treated with DTG + 3TC compared to TBR.	Change from baseline in biomarkers of ~~inflammation, mitochondrial function and~~ telomerase ~~activity~~ at Week 48

Current Text:

To evaluate biomarkers of **telomerase function** in a subset of subjects treated with DTG + 3TC compared to TBR.	Change from baseline in biomarkers of **telomerase function** at **Weeks 48 and 96**

Previous Text:

To evaluate the longer term antiviral and immunological effects, safety and tolerability of DTG + 3TC once daily in subjects treated with DTG + 3TC since the Early Switch Phase	For subjects in the DTG + 3TC arm since Early Switch Phase: • Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 96 using the Snapshot algorithm for the ITT-E population • Change from Baseline in CD4+ lymphocyte count at Week 96 • Incidence and severity of AEs and laboratory abnormalities over 96 weeks • Proportion of subjects who discontinue treatment due to AEs over 96 weeks • Incidence of disease progression (HIV associated conditions, AIDS and death) through Week 96

	• Change from Baseline in renal, bone ~~**and cardiovascular**~~ biomarkers at Week 96

Current Text:

To evaluate the longer term antiviral and immunological effects, safety and tolerability of DTG + 3TC once daily in subjects treated with DTG + 3TC since the Early Switch Phase	For subjects in the DTG + 3TC arm since Early Switch Phase: • Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 96 using the Snapshot algorithm for the ITT-E population • Change from Baseline in CD4+ lymphocyte count at Week 96 • Incidence and severity of AEs and laboratory abnormalities over 96 weeks • Proportion of subjects who discontinue treatment due to AEs over 96 weeks • Incidence of disease progression (HIV associated conditions, AIDS and death) through Week 96 • Change from Baseline in renal and bone, biomarkers at Week 96

Previous Text:

To evaluate the antiviral and immunological effects, safety and tolerability of DTG + 3TC for subjects switching in the Late Switch Phase	For subjects switching to DTG + 3TC in the Late Switch Phase: • Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 96 using the Snapshot algorithm for the ITT-E population • Change from Baseline in CD4+ lymphocyte count at Week 96 • Incidence and severity of AEs and laboratory abnormalities during the Late Switch Phase • Proportion of subjects who discontinue treatment due to AEs during the Late Switch Phase • Incidence of disease progression (HIV associated conditions, AIDS and death) during the Late Switch Phase • Change from Baseline in renal, bone ~~**and cardiovascular**~~ biomarkers at Week 96

Current Text:

To evaluate the antiviral and immunological effects, safety and tolerability of DTG + 3TC for subjects switching in the Late Switch Phase	For subjects switching to DTG + 3TC in the Late Switch Phase: • Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 96 using the Snapshot algorithm for the ITT-E population • Change from Baseline in CD4+ lymphocyte count at Week 96 • Incidence and severity of AEs and laboratory abnormalities during the Late Switch Phase • Proportion of subjects who discontinue treatment due to AEs during the Late Switch Phase • Incidence of disease progression (HIV associated conditions, AIDS and death) during the Late Switch Phase • Change from Baseline in renal and bone biomarkers at Week 96

- **Section 4.1. Overall Design:**

Previous Text:

All subjects who successfully complete up to 100 weeks of treatment will have the opportunity to continue receiving these agents until either DTG + 3TC FDC is locally approved and commercially available, they no longer derive clinical benefit, they meet a protocol-defined reason for discontinuation, or until development of DTG + 3TC dual regimen is terminated.

Current Text:

All subjects who successfully complete up to 100 weeks of treatment will have the opportunity to continue receiving DTG + 3TC FDC once daily in a Continuation Phase, as outlined in Section 4.2.4.

Section 5.1. Inclusion Criteria #5:

Previous Text:

Must be on uninterrupted ART for at least 6 months prior to screening. Only the following regimens are allowed:

Subjects on a TAF-based regimen for at least 6 months, or

Subjects who switched from TDF (as part of first-line regimen) to TAF, without any changes to the other drugs in their regimen, and have been on the TAF-based regimen for at least 3 months immediately prior to Screening. The switch must have occurred due to tolerability/safety, access to medications, or convenience/simplification, and must NOT have been done for suspected or established treatment failure.

Current Text:

Must be on uninterrupted ART for at least 6 months prior to screening. Only the following regimens are allowed:

Subjects on a TAF-based regimen for at least 6 months **as the initial regimen**, or

Subjects who switched from **a TDF first regimen** to TAF, without any changes to the other drugs in their regimen, and have been on the TAF-based regimen for at least 3 months immediately prior to Screening**, i.e., the only switch made is from TDF to TAF.** This switch must have occurred due to tolerability/safety, access to medications, or convenience/simplification, and must NOT have been done for suspected or established treatment failure. **A switch from a PI boosted with RTV to the *same* PI boosted with cobicistat is allowed, and vice versa.**

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

Removed text: "The TBR comparators will be considered investigational medicinal product medicinal product: a pharmaceutical form of an active substance being tested or used as a reference in a clinical trial."

- **Section 6.2. Protocol Permitted Substitutions:**

New Section added for clarification on use of pharmacokinetic boosters.

- New text added: A switch from a PI boosted with RTV to the same PI boosted with cobicistat is allowed. A switch from a PI boosted with cobicistat to the same PI boosted with RTV is allowed. **Section 7.1. Table 2 Time and Events Table:**

    - Footnote 'o' regarding plasma samples revised for clarity.

- 'Whole Blood' entry was separated into two rows: 'Whole Blood (Virology)' and 'Whole Blood (Telomere length)' to distinguish the samples by the intended use. In addition the word 'PBMCs' was removed.

- 'PBMCs' entry was changed to 'Cryopreserved PBMCs' to specify that the PBMC sample must be cryopreserved for the evaluation of telomerase activity.

- Footnote 'w' was revised to clarify that whole blood samples (instead of PBMCs) may be used for virologic analyses as described in the protocol. Sample collection timepoints are indicated in the T&E table and were removed from the footnote.

- An additional footnote 'x' was created for the new entry Whole Blood (Telomere length) specifying that the sample will be used for telomere length evaluations.

- Footnote 'y' (previously footnote 'x') specifies that PBMCs (instead of plasma) will be collected, cryopreserved, and stored for a subset of sites. Additional revisions were made to clarify that these samples will be used for the measurement of telomerase activity only.

- Footnote 'z' (previously footnote 'y') was renamed due to the creation of the above footnote 'x'.

- **Section 7.3.1.3. Exploratory Efficacy Endpoints:**

Additional text regarding exploratory efficacy endpoints was added:

Additional exploratory efficacy endpoints for subjects treated with DTG + 3TC since the Early Switch Phase, and for subjects switching in the Late Switch Phase include:

- Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 96 using the Snapshot algorithm for the ITT-E population
- Change from Baseline in CD4+ lymphocyte count at Week 96
- Incidence of disease progression (HIV associated conditions, AIDS and death) through Week 96.

- **Section 7.5. Other Biomarkers:**

Previous text:

In a subset of subjects and at sites that can collect these samples, PBMCs and plasma will be collected, cryopreserved and stored at baseline and at Weeks 48 and 96. ~~PBMCs and plasma will be analyzed for various markers of inflammation, mitochondrial and telomerase activity/function. Changes from baseline in these measurements will be compared between the DTG + 3TC and TBR arms.~~

Current text:

- Whole blood will be used for measurement of telomere length.

- In a subset of sites, PBMCs will be collected, cryopreserved and stored for measurement of telomerase activity.

Previous text:

Since the intention is to utilize these biomarkers for research purposes, the Sponsor will not be reporting real time results of these assessments to the investigator except for Cystatin C (Day 1 only) and 25 hydroxy-vitamin D.

Current text:

Since the intention is to utilize these biomarkers for research purposes **and the clinical significance of these results is uncertain**, the Sponsor will not be reporting real time results of these assessments to the investigator except for Cystatin C (Day 1 only) and 25 hydroxy-vitamin D.

- **Section 12.9. Appendix 9:**

Updated the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events from Version 2.0 (November 2014) to Version 2.1 (March 2017).

- **Section 12.10. Appendix 10:**

Additional Level 2 headers in this Section, and added new Section 12.10.2:

- **12.10.2 Japan**

All drug will be provided centrally. For subjects receiving Descovy as their TBR in Japan, the baseline third agent choice must be DTG.

13.11.2. Protocol changes for Amendment 02 (2017-JUN-13) from Amendment 01 (2017-MAY-16): A global amendment applicable to all participating countries

Summary of Key Changes in Protocol Amendment 02

- Clarification was provided that a switching from a PI boosted with ritonavir to the same PI boosted with cobicistat and vice versa is allowed during the study (Section 1). These agents are expected to have similar boosting effect and no impact on overall efficacy of the regimen.
- Text related to the retesting of subjects with HIV-1 RNA <50 c/mL at Week 48 was removed because only subjects with HIV-1 RNA ≥50 c/mL at Week 48 will be retested (Section 4.2.2).
- The screening criteria related to hepatitis B status were corrected in the risk assessment table (Section 4.6.1).

- Relevant text throughout the protocol was edited to make it clear that the review of genotypic resistance testing results (for both NRTI and DTG resistance mutations) by ViiV Virology is required after screening and before randomization (see Section 4.6.1, Section 5.2, Section 7.1 and Section 7.2.1). The prior text implied that this review was optional and/or that it only applied to DTG resistance-associated mutations.

- The exclusion criteria were updated to make it clear that any evidence of major NRTI mutation or presence of any DTG resistance-associated mutations must be provided to ViiV after screening and before randomization (Section 5.2). The prior text implied that only DTG resistance-associated mutations be provided. The same clarification was made in footnote 'e' of the Time and Events Table (Section 7.1) and in the Screening Assessments section (Section 7.2.1).

- The inclusion criteria for pregnancy testing were updated to be consistent with the Time and Events Table. Specifically, a local serum hCG test is allowed at randomization if results can be obtained 24 hours prior to randomization (Section 5.1).

- The missing connector words, 'or anticipated need', were added to the exclusion criteria related to HCV therapy (Section 5.2).

- Text was updated to allow the use of local labs in exceptional circumstances, only if central lab results cannot be generated (plasma HIV-1 RNA levels are excluded from this allowance and must come from a central lab). In this case, the local lab results must be reviewed by the Medical Monitor (Section 5.3). Based on prior experience with studies in similar regions, ViiV Healthcare will allow this exception for study feasibility purposes. This same change was made to the Clinical Safety Laboratory Assessments text (Section 7.4.6).

- The blinding section was updated to reflect the open-label design of the study (Section 6.5). Prior text had conflicting language indicating that some aspects of the study were blinded. An additional reference to blinding was removed from Appendix 2 (see Section 12.2.1.3).

- The Screening Assessments text related to syphilis treatment was clarified because the prior text was unclear (Section 7.2.1).

- The Vital Signs section was corrected to be consistent with the planned assessments outlined in the Time and Events Table (Section 7.4.4).

- Methods for GFR estimates were updated in Table 1 (required safety labs). Specifically, GFR will be estimated using the CKD-EPI-cystatin C equation in addition to the CKD-EPI-creatinine equation (Section 7.4.6).

- The Analysis Data Sets text (Section 9.3.2) was updated to clarify that a switch from a PI boosted with ritonavir to the same PI boosted with cobicistat (and vice versa) is permitted per protocol and will not be considered as a change in background ART hence, will not incur a penalty in the Snapshot algorithm. These

agents are expected to have similar boosting effect and no impact on overall efficacy of the regimen.

- Appendix 5 (Liver Safety – Required Actions and Follow-up Assessments): The appendix was updated to be consistent with ViiV Healthcare's required assessments which are appropriate for this patient population. The prior appendix was based on a general GSK set of assessments and was not appropriate.
- Appendix 6 (Liver Safety – Study Treatment Restart Guidelines): The appendix was updated to be consistent with ViiV Healthcare's guidelines which are appropriate for this patient population. The prior appendix was based on a general GSK set of assessments and was not appropriate.
- Appendix 8 (Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events): The appendix was updated to be consistent with ViiV Healthcare's definitions and procedures. The prior appendix was based on a general GSK template and was not appropriate.
- Throughout the protocol, references to GSK were changed to ViiV, PPD, ViiV/GSK, or ViiV/GSK/PPD in order to indicate the appropriate roles and responsibilities of each entity.
- Additional minor revisions were made to the text to correct errors and improve accuracy.

13.11.3. Protocol changes for Amendment 03 (2017-AUG-24) from Amendment 02 (2017-JUN-13): A global amendment applicable to all participating countries

Summary of Key Changes in Protocol Amendment 03 and Rationale

- Reduction in Sample size from a total of 766 randomized subjects to 550 randomized subjects based on reassessment of the statistical assumptions and the use of a more accurate expected value for the primary endpoint of the investigational arm.
- Addition of assessment of CD8+ lymphocyte cell counts at Baseline, Week 24, Week 48 and Week 96. Based on external expert advice.
- Addition of assessment of inflammation biomarkers at Baseline, Week 48 and Week 96 as a new exploratory endpoint. Based on external expert advice.
- Specification of the minimum 25 years retention from the issue of the final Clinical Study Report (CSR) or equivalent summary for the Investigator Site Files to align with the most recent Sponsor standard operating procedure.

List of Specific Changes

Title Page. Authors

Previous text:

PPD [redacted]

Current text:

PPD [redacted]

Section 1. Objective(s)/Endpoints:

Previous text:

To evaluate the immune effects of DTG + 3TC once daily compared to continuation of TBR	• Change from Baseline in CD4+ cell count at Weeks 24 and 48 • Incidence of disease progression (HIV-associated conditions, AIDS, and death) through Weeks 24 and 48

Current text:

To evaluate the immune effects of DTG + 3TC once daily compared to continuation of TBR	• Change from Baseline in CD4+ cell count **and in CD4+/CD8+ cell counts ratio** at Weeks 24 and 48 • Incidence of disease progression (HIV-associated conditions, AIDS, and death) through Weeks 24 and 48

Section 1. Overall Design:

Previous text:

Approximately ~~**766**~~ HIV-1 infected adults who are on a stable TBR will be randomized 1:1 to switch to DTG + 3TC once daily (DTG + 3TC arm) for up to 100 weeks, or to continue their TBR for 52 weeks, at which time and if HIV1 RNA <50 c/mL at Week 48 (or upon retest by Week 52), these subjects will switch to DTG + 3TC up to Week 100.

The sample size is such that the study has 90% power to demonstrate non-inferiority using a 4% margin, assuming a true ~~**3**~~ % virologic failure rate at Week 48 and using a 2.5% one-sided alpha level.

Current text:

Approximately **550** HIV-1 infected adults who are on a stable TBR will be randomized 1:1 to switch to DTG + 3TC once daily (DTG + 3TC arm) for up to 100 weeks, or to continue their TBR for 52 weeks, at which time and if HIV1 RNA <50 c/mL at Week 48 (or upon retest by Week 52), these subjects will switch to DTG + 3TC up to Week 100.

The sample size is such that the study has 90% power to demonstrate non-inferiority using a 4% margin, assuming a true **2** % virologic failure rate at Week 48 and using a 2.5% one-sided alpha level.

Section 1. Type and Number of Subjects:

Previous text:

Assuming 30% screen failure rate, approximately ~~**1100**~~ HIV-1-infected adult subjects will be screened to achieve ~~**766**~~ randomized subjects for a total of ~~**383**~~ evaluable subjects per treatment group.

Current text:

Assuming 30% screen failure rate, approximately **800** HIV-1-infected adult subjects will be screened to achieve **550** randomized subjects for a total of **275** evaluable subjects per treatment group.

Section 2.2. Brief Background:

Previous text:

One such study was the OLE study which was an open label study in virologically suppressed HIV-1 infected individuals (HIV-1 RNA < 50 copies/mL) receiving a lopinavir (LPV)/r plus 3TC or emtricitabine (FTC) containing 3-drug regimen who were randomized to continue their current triple based regimen or have their therapy simplified to a dual regimen of LPV/r + 3TC ~~**or FTC**~~ [Arribas, 2015]. The primary endpoint was the proportion of patients free of therapeutic failure at 48 weeks. In a modified Intent to Treat (m-ITT) analysis, dual therapy with LPV/r + 3TC ~~**or FTC**~~ demonstrated non-inferior efficacy and comparable safety to LPV/r + 2 NRTIs, as maintenance therapy in virologically suppressed patients (91.5% vs. 90.9% respectively; 95% Confidence Interval (CI): -0.6% to 8.1%).

Current text:

One such study was the OLE study which was an open label study in virologically suppressed HIV-1 infected individuals (HIV-1 RNA < 50 copies/mL) receiving a lopinavir (LPV)/r plus 3TC or emtricitabine (FTC) containing 3-drug regimen who were

randomized to continue their current triple based regimen or have their therapy simplified to a dual regimen of LPV/r + 3TC [Arribas, 2015]. The primary endpoint was the proportion of patients free of therapeutic failure at 48 weeks. In a modified Intent to Treat (m-ITT) analysis, dual therapy with LPV/r + 3TC demonstrated non-inferior efficacy and comparable safety to LPV/r + 2 NRTIs, as maintenance therapy in virologically suppressed patients (91.5% vs. 90.9% respectively; 95% Confidence Interval (CI): -0.6% to 8.1%).

Section 3. Objective(s) and Endpoint (s):

Previous text:

To evaluate the immune effects of DTG + 3TC once daily compared to continuation of TBR	• Change from Baseline in CD4+ cell count at Weeks 24 and 48 • Incidence of disease progression (HIV-associated conditions, AIDS, and death) through Weeks 24 and 48

Current text:

To evaluate the immune effects of DTG + 3TC once daily compared to continuation of TBR	• Change from Baseline in CD4+ cell count **and in CD4+/CD8+ cell counts ratio** at Weeks 24 and 48 • Incidence of disease progression (HIV-associated conditions, AIDS, and death) through Weeks 24 and 48

Previous text:

Exploratory	
To evaluate the effect of patient characteristics (e.g., demographic factors, Baseline CD4) on antiviral and immunological responses to DTG + 3TC compared to TBR	• Proportion of subjects by subgroup(s) (e.g., by age, gender, Baseline CD4) with snapshot virologic failure at Weeks 24 and 48 • Change from Baseline in CD4+ cell counts at Weeks 24 and 48 by patient subgroups
To asses willingness to switch for subjects treated with DTG + 3TC compared to TBR	Reasons for Willingness to Switch at Day 1
To evaluate biomarkers of telomerase function in a subset of subjects treated with DTG + 3TC compared to TBR.	Change from baseline in biomarkers of telomerase function at Weeks 48 and 96
To evaluate the longer term antiviral and immunological effects, safety and tolerability of DTG + 3TC once daily in subjects treated with DTG + 3TC since the Early Switch Phase	For subjects in the DTG + 3TC arm since Early Switch Phase: • Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 96 using the Snapshot algorithm for the ITT-E population

	• Change from Baseline in CD4+ lymphocyte count at Week 96 • Incidence and severity of AEs and laboratory abnormalities over 96 weeks • Proportion of subjects who discontinue treatment due to AEs over 96 weeks • Incidence of disease progression (HIV associated conditions, AIDS and death) through Week 96 • Change from Baseline in renal and bone biomarkers at Week 96
To evaluate the antiviral and immunological effects, safety and tolerability of DTG + 3TC for subjects switching in the Late Switch Phase	For subjects switching to DTG + 3TC in the Late Switch Phase: • Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 96 using the Snapshot algorithm for the ITT-E population • Change from Baseline in CD4+ lymphocyte count at Week 96 • Incidence and severity of AEs and laboratory abnormalities during the Late Switch Phase • Proportion of subjects who discontinue treatment due to AEs during the Late Switch Phase • Incidence of disease progression (HIV associated conditions, AIDS and death) during the Late Switch Phase • Change from Baseline in renal and bone biomarkers at Week 96

Current text:

Exploratory	
To evaluate the effect of patient characteristics (e.g., demographic factors, Baseline CD4) on antiviral and immunological responses to DTG + 3TC compared to TBR	• Proportion of subjects by subgroup(s) (e.g., by age, gender, Baseline CD4) with snapshot virologic failure at Weeks 24 and 48 • Change from Baseline in CD4+ cell counts at Weeks 24 and 48 by patient subgroups
To asses willingness to switch for subjects treated with DTG + 3TC compared to TBR	Reasons for Willingness to Switch at Day 1
To evaluate biomarkers of telomerase function in a subset of subjects treated with DTG + 3TC compared to TBR.	Change from baseline in biomarkers of telomerase function at Weeks 48 and 96

To evaluate inflammation biomarkers in a subset of subjects treated with DTG+ 3TC compared to TBR	**Change from Baseline in inflammation biomarkers at Weeks 48**
To evaluate the longer term antiviral and immunological effects, safety and tolerability of DTG + 3TC once daily in subjects treated with DTG + 3TC since the Early Switch Phase	For subjects in the DTG + 3TC arm since Early Switch Phase: • Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 96 using the Snapshot algorithm for the ITT-E population • Change from Baseline in CD4+ lymphocyte count **and in CD4+/CD8+ cell count ratio** at Week 96 • Incidence and severity of AEs and laboratory abnormalities over 96 weeks • Proportion of subjects who discontinue treatment due to AEs over 96 weeks • Incidence of disease progression (HIV associated conditions, AIDS and death) through Week 96 • Change from Baseline in renal and bone biomarkers at Week 96 • **Change from baseline in biomarkers of inflammation and telomerase function at week 96**
To evaluate the antiviral and immunological effects, safety and tolerability of DTG + 3TC for subjects switching in the Late Switch Phase	For subjects switching to DTG + 3TC in the Late Switch Phase: • Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 96 using the Snapshot algorithm for the ITT-E population • Change from Baseline in CD4+ lymphocyte count **and in CD4+/CD8+ cell count ratio** at Week 96 • Incidence and severity of AEs and laboratory abnormalities during the Late Switch Phase • Proportion of subjects who discontinue treatment due to AEs during the Late Switch Phase • Incidence of disease progression (HIV associated conditions, AIDS and death) during the Late Switch Phase • Change from Baseline in renal and bone biomarkers at Week 96 • **Change from baseline in biomarkers of inflammation and telomerase function at week 96**

Section 4.1. Overall Design

Previous text:

Approximately ~~**766**~~ HIV-1 infected adults who are on a stable TBR will be randomized 1:1 to switch to DTG + 3TC once daily (DTG + 3TC arm) for up to 100 weeks, or to continue their TBR for 52 weeks, at which time and if HIV-1 RNA <50 c/mL at Week 48 (or upon retest by Week 52), these subjects will switch to DTG + 3TC up to Week 100.

Current text:

Approximately **550** HIV-1 infected adults who are on a stable TBR will be randomized 1:1 to switch to DTG + 3TC once daily (DTG + 3TC arm) for up to 100 weeks, or to continue their TBR for 52 weeks, at which time and if HIV-1 RNA <50 c/mL at Week 48 (or upon retest by Week 52), these subjects will switch to DTG + 3TC up to Week 100.

Section 4.3. Type and Number of Subjects

Previous text:

The target population to be enrolled is HIV-1 infected adults who are virologically suppressed on a TBR (~~**either**~~ as a first- ~~**or second**~~ line regimen) and with no evidence or history of ARV drug-resistance.

Current text:

The target population to be enrolled is HIV-1 infected adults who are virologically suppressed on a TBR (As a first-line regimen **with specific allowed switches as defined in inclusion criterion 5**) and with no evidence or history of ARV drug-resistance.

Previous text:

Assuming 30% screen failure rate, approximately ~~**1100**~~ HIV-1-infected adult subjects will be screened to achieve ~~**766**~~ randomized subjects for a total of ~~**383**~~ evaluable subjects per treatment group.

Current text:

Assuming 30% screen failure rate, approximately **800** HIV-1-infected adult subjects will be screened to achieve **550** randomized subjects for a total of **275** evaluable subjects per treatment group.

Section 5.1. Inclusion Criteria

Inclusion criterion 6:

Previous text: 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 Section 12.3) from 30 days prior to the first dose of

study medication ~~**and until 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.

Current text:

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 Section 12.3) 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.

Section 5.2. Exclusion Criteria Exclusion criterion 14

Previous text:

Use of any regimen consisting of single or dual ART (~~**including peri-partum treatment with nevirapine)**~~.

Current text;

Use of any regimen consisting of single or dual ART.

Exclusion criterion 15

Previous text:

Any evidence of major NRTI mutation or presence of any ~~**DTG**~~ resistance-associated mutation [Wensing, 2017] in any available prior resistance genotype assay test result, if known, *must* be provided to ViiV after screening and before randomization for review by ViiV Virology. Refer to the most recent version of IAS Guidelines, SPM, and Section 7.2.1 (Screening Assessments) for more information.

Current text:

Any evidence of major NRTI mutation or presence of any **major INSTI** resistance-associated mutation [Wensing, 2017] in any available prior resistance genotype assay test result, if known, *must* be provided to ViiV after screening and before randomization for review by ViiV Virology. Refer to the most recent version of IAS Guidelines, SPM, and Section 7.2.1 (Screening Assessments) for more information.

Section 7.1. Time and Events Table:

New assessment row:

Added a row of vital sign procedure of body weight and calculated BMI at all visits.

Lymphocyte subset:

Previous text:

Lymphocyte subset

Current text:

Lymphocyte subset **(CD4+ at all visits and CD8+ at Baseline, and Weeks 24, 48 and 96 only)**

Added a row under Laboratory Assessment:

Previous text:

None

Current text:

Inflammation biomarkers (blood)[aa] with assessement at Baseline, Week 48, Week 96 and Withdrawal. Footnote aa specifies the biomarkers as follows: Blood sample for inflammation biomarker assessments: IL-6, hs-CRP, d dimer, sCD14, sCD163.

Footnote q was edited and added to the withdrawal visit assessment of the renal and bone markers analytes.

Previous text:

Collect ~~**fasting lipids and glucose**~~ if the Withdrawal visit occurs at Week 48 or 96.

Current text:

Collect **sample for these assessments ONLY** if the Withdrawal visit occurs at **Week 24,** 48 or 96

Additional footnote was added to the withdrawal visit assessment of the Whole blood (telomere Length), Cryopreserved PBMCs and Inflammation biomarkers.

Previous text:

None.

Current text:

Collect sample for these assessments ONLY if the Withdrawal visit occurs at Week 48 or 96

Section 7.3.1. Efficacy Evaluations

Lymphocyte subsets:

Previous text:

Lymphocyte subsets will be collected for assessment by flow cytometry (total lymphocyte counts, percentage, and absolute CD4+ lymphocyte counts) according to the Time and Events Table (Section 7.1).

Current text:

Lymphocyte subsets will be collected for assessment by flow cytometry (total lymphocyte counts, percentage, and absolute CD4+ **and CD8+** lymphocyte counts) according to the Time and Events Table (Section 7.1).

Section 7.3.1.2. Secondary Efficacy Endpoints

Previous text:

None

Current text:

Change from Baseline in CD8+ lymphocyte count and CD4+/CD8+ cell counts ratio at Weeks 24 and 48

Section 7.3.1.3. Exploratory Efficacy Endpoints

Previous text:

Change from Baseline in CD4+ lymphocyte count at Week 96

Current text:

Change from Baseline in CD4+ **and CD8+** lymphocyte count **and CD4+/CD8+ cell counts ratio** at Week 96

Section 7.4.4. Vital Signs

Previous text:

At the Screening visit, vital signs will be measured in semi-supine position after 5 minutes rest and will include height, weight, systolic and diastolic blood pressure and Body Mass Index (BMI).

Current text:

At the Screening visit, vital signs will be measured in semi-supine position after 5 minutes rest and will include height, weight, systolic and diastolic blood pressure and Body Mass Index (BMI). **Body weight and BMI will also be assessed at each visit according to the Time and Events Table (Section 7.1).**

Section 7.4.6. Table 1, Other Tests:

Previous text:

CD4+ lymphocyte counts

Current text:

CD4+ lymphocyte counts **and percent**
CD8+ lymphocyte counts, percent and CD4+/CD8+ cell counts ratio at Baseline and Weeks 24, 48 and 96.

Previous text:

None

Current addition:

Inflammation biomarkers including IL-6, hs CRP, d dimer, sCD14 and sCD163[g].

Updated footnote g with definition of the inflammation biomarkers abbreviations: **Il-6 = interleukin-6, hs-CRP = high-sensitivity C reactive protein, sCD = soluble CD.**

Section 7.5. Biomarkers:

Previous text:

Blood and urine are being collected to perform renal and bone biomarker assessments. In addition to measurements of serum creatinine, estimated GFR, and urinary excretion of albumin, protein, creatinine and phosphate, additional renal biomarkers include:

Renal biomarkers:

- Cystatin C (blood),
- Retinol Binding Protein (RBP, blood/urine)
- Beta-2-Microglobulin (B2M, blood/urine).

Bone biomarkers:

- Bone-specific alkaline phosphatase
- Procollagen type 1 N-propeptide
- Type 1 collagen cross-linked C-telopeptide
- Osteocalcin
- 25 hydroxy-Vitamin D

~~**Other Biomarkers**~~:

- Whole blood will be used for measurement of telomere length.

In a subset of sites, PBMCs will be collected, cryopreserved and stored for measurement of telomerase activity.

Current text:

Blood and urine are being collected to perform renal and bone biomarker assessments. In addition to measurements of serum creatinine, estimated GFR, and urinary excretion of albumin, protein, creatinine and phosphate, additional renal biomarkers include:

Renal biomarkers:

- Cystatin C (blood),
- Retinol Binding Protein (RBP, blood/urine)
- Beta-2-Microglobulin (B2M, blood/urine).

Bone biomarkers:

- Bone-specific alkaline phosphatase
- Procollagen type 1 N-propeptide
- Type 1 collagen cross-linked C-telopeptide
- Osteocalcin
- 25 hydroxy-Vitamin D

Blood is being collected to perform assessments of biomarkers of inflammation and telomere function.

Inflammation biomarkers:

- **Interleukin-6 (IL-6)**
- **High-sensitivity C reactive protein (hs-CRP)**
- **D-dimer**
- **Soluble CD14 (sCD14)**
- **Soluble CD163 (sCD163)**

Telomere function:

- Whole blood will be used for measurement of telomere length.

In a subset of sites, PBMCs will be collected, cryopreserved and stored for measurement of telomerase activity.

Section 9.2. Sample Size Considerations.

Previous text:

Assuming a true ~~3~~% virologic failure rate in each arm, a non-inferiority margin of 4%, and a 2.5% one-sided significance level, this study requires ~~383~~ subjects per treatment arm.

This would provide 9~~0~~% power to show non-inferiority for the proportion of subjects with virologic failure according to the FDA snapshot algorithm at 48 weeks post-switch. If we observed a ~~3~~% virologic failure rate for the non-switch subjects then non-inferiority would be declared if the observed treatment difference was less than 1.4 percentage points.

9.2.1.1. Rationale for non-inferiority margin

According to the FDA's 2015 guidance document (Human Immunodeficiency Virus-1 Infection: Development of ART Drugs for Treatment, November 2015), the margin for switch trials is driven by the largest clinically tolerable virologic failure rate. Per the FDA document, typical rates of virological failure seen in switch studies range from 1 to 3 percent and a margin of 4% for virologic failure rate is considered tolerable. Assuming 2% virologic failure rate in both treatment arms, a 4% non-inferiority margin is considered comparable to a 10% to 12% non-inferiority margin using response rate as endpoint. A margin of 4% was e chosen for the present study assuming ~~3~~% failure rate in both arms~~**, which is more stringent than assuming 2% failure rate in both arms**~~ [CDER, 2015].

9.2.1.2. Response rate assumptions

Table 2 shows Snapshot response rates and Snapshot virologic failure rates in previous switch studies in HIV-1 infected ART-experienced subjects. Taken together, these data suggest that a reasonable assumption for the true failure rate for the current ART control arm and the switch arm is ~~3~~%.

Table 2 Snapshot Response rates in previous switch studies

Week 48			
Study	**Treatment Arm**	**HIV-1 RNA <50**	**Virologic Failure**
SPIRIT[a,b]	RPV/FTC/TDF	89%	8/317 (2.5%)
STRATEGY-PI[c]	QUAD	94%	2/290 (<1%)
	PI + FTC/TDF	87%	2/139 (1%)
STRATEGY-NNRTI[d]	QUAD	93%	3/290 (1%)
	NNRTI + FTC/TDF	88%	1/143 (<1%)
SALT[e]	ATV/r+3TC	77%	Not available[f]
	ATV/r+2NRTIs	76%	Not available[f]
OLE[g]	LPV/r+3TC	88%	Not available[h]
	LPV/r+TDF/FTC or ABC/3TC	87%	Not available[h]
GS-292-0109[i]	E/C/F/TAF	97%	10/959 (1%)
	TDF-based regimen[j]	93%	6/477 (1%)
GS-US-311-1089[k]	TAF containing regimen	94%	1/333 (<1%)
	TDF regimen	93%	5/330 (2%)
Week 24			
STRIIVING[l]	DTG + ABC/3TC STR	85%	1%
	Current ART	88%	1%

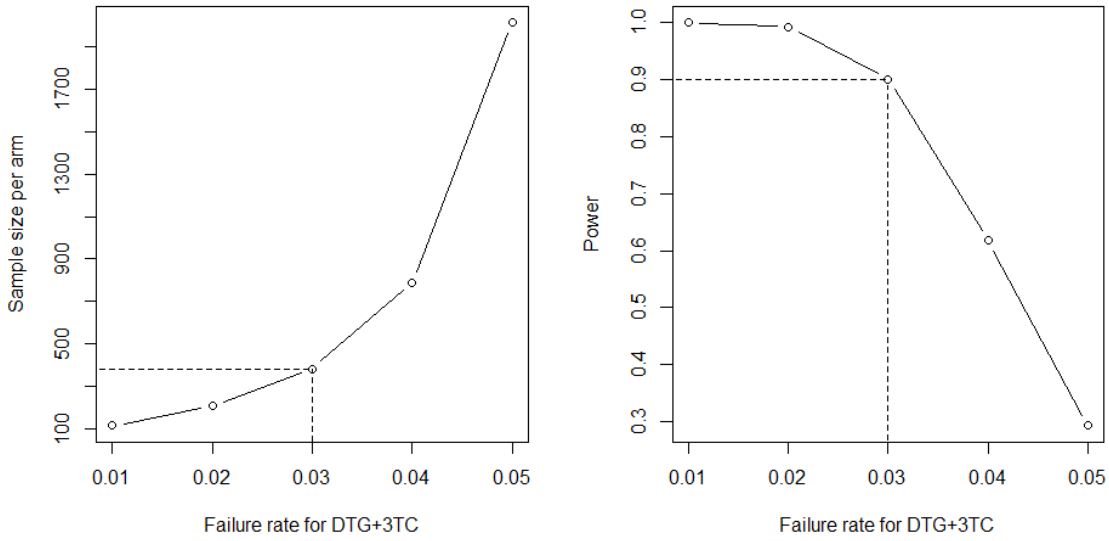
a. [Palella, 2014]
b. Participants in the PI/r +2 NRTIs arm were switched to RPV/FTC/TDF at Week 24; therefore Week 48 response data are not available for this treatment group.
c. [Arribas, 2014]
d. [Pozniak, 2014]
e. [Perez-Molina, 2015]
f. The percentage of snapshot virologic failure is not available; however, 4% in the dual arm and 3% in the cART arm had protocol defined virologic failure (PDVF).
g. [Arribas, 2015]
h. The percentage of snapshot virologic failure is not available; however, 2% per arm had PDVF.
i. [Mills, 2016]
j. EVG/Cobistat/TDF/FTC, EFV/TDF/FTC, ATV/Cobistat/TDF/FTC, or RTV/ATV/TDF/FTC
k. [Gallant, 2016]

l. [TRottier, 2015]

9.2.2. Sample Size Sensitivity

Figure 3 shows sensitivity of the required sample size to the true response rate for the DTG + 3TC arm assuming a ~~3~~% failure rate in the current ART non-switch arm and a 4% margin.

Figure 3 Sample size sensitivity for the Snapshot Virologic Failure



Power=90%, NI margin=4%, control arm failure rate=3% N=383 per arm, NI margin=4%, control arm failure rate=3%

Current text:

9.2.1. Sample Size Assumptions

Assuming a true **2**% virologic failure rate in each arm, a non-inferiority margin of 4%, and a 2.5% one-sided significance level, this study requires **275** subjects per treatment arm.

This would provide **92**% power to show non-inferiority for the proportion of subjects with virologic failure according to the FDA snapshot algorithm at 48 weeks post-switch.

If we observed a **2**% virologic failure rate for the non-switch subjects then non-inferiority would be declared if the observed treatment difference was less than **or equal to 1.24** percentage points.

9.2.1.1. Rationale for non-inferiority margin

According to the FDA's 2015 guidance document (Human Immunodeficiency Virus-1 Infection: Development of ART Drugs for Treatment, November 2015), the margin for switch trials is driven by the largest clinically tolerable virologic failure rate. Per the FDA document, typical rates of virological failure seen in switch studies range from 1 to 3 percent and a margin of 4% for virologic failure rate is considered tolerable. Assuming 2% virologic failure rate in both treatment arms, a 4% non-inferiority margin is considered comparable to a 10% to 12% non-inferiority margin using response rate as endpoint. A margin of 4% was therefore chosen for the present study assuming **2**% failure rate in both arms [CDER, 2015].

9.2.1.2. Response **and Virological Failure** rate assumptions

Table 2 shows Snapshot response **(HIV-1 RNA <50 c/mL)** rates and Snapshot virologic failure **(HIV-1 RNA ≥50 c/mL)** rates in previous switch studies in HIV-1 infected ART-experienced subjects. Taken together, these data suggest that a reasonable assumption for the true failure rate for the current ART control arm and the switch arm is **2**%.

Table 2 Snapshot Response **and Virological Failure** rates in previous switch studies

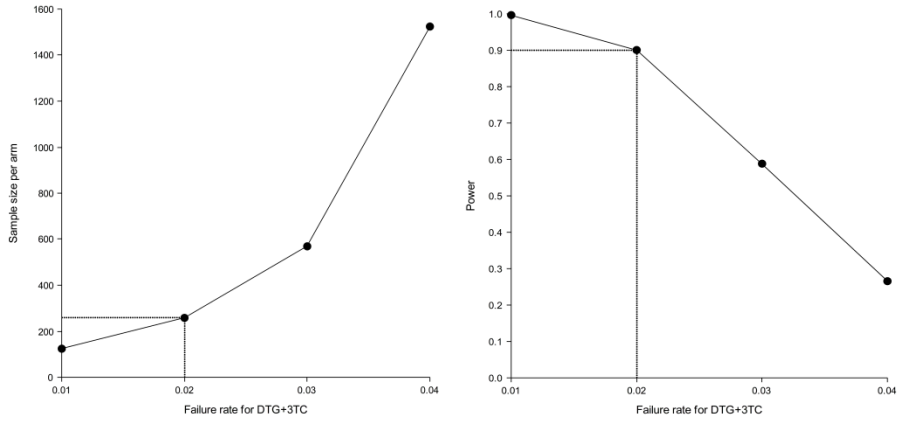
Week 48			
Study	**Treatment Arm**	**Response Rate (HIV-1 RNA <50 c/mL)**	Virologic Failure **(HIV-1 RNA ≥50 c/mL)**
SPIRIT[a,b]	RPV/FTC/TDF	89%	8/317 (2.5%)
STRATEGY-PI[c]	QUAD	94%	2/290 (<1%)
	PI + FTC/TDF	87%	2/139 (1%)
STRATEGY-NNRTI[d]	QUAD	93%	3/290 (1%)
	NNRTI + FTC/TDF	88%	1/143 (<1%)
SALT[e]	ATV/r+3TC	77%	Not available[f]
	ATV/r+2NRTIs	76%	Not available[f]
OLE[g]	LPV/r+3TC	88%	Not available[h]
	LPV/r+TDF/FTC or ABC/3TC	87%	Not available[h]
GS-292-0109[i]	E/C/F/TAF	97%	10/959 (1%)
	TDF-based regimen[j]	93%	6/477 (1%)
GS-US-311-1089[k]	TAF containing regimen	94%	1/333 (<1%)
	TDF regimen	93%	5/330 (2%)
SWORD 1 & 2[l]	**CAR**	**95%**	**6/511 (1%)**
	DTG+RPV	**95%**	**3/513 (<1%)**
Week 24			
STRIIVING[m]	DTG + ABC/3TC STR	85%	1%
	Current ART	88%	1%

a. [Palella, 2014]
b. Participants in the PI/r +2 NRTIs arm were switched to RPV/FTC/TDF at Week 24; therefore Week 48 response data are not available for this treatment group.
c. [Arribas, 2014]
d. [Pozniak, 2014]
e. [Perez-Molina, 2015]
f. The percentage of snapshot virologic failure is not available; however, 4% in the dual arm and 3% in the cART arm had protocol defined virologic failure (PDVF).
g. [Arribas, 2015]
h. The percentage of snapshot virologic failure is not available; however, 2% per arm had PDVF.
i. [Mills, 2016]
j. EVG/Cobistat/TDF/FTC, EFV/TDF/FTC, ATV/Cobistat/TDF/FTC, or RTV/ATV/TDF/FTC
k. [Gallant, 2016]
l. [Libre, 2017]
m. [Trottier, 2015]

9.2.2. Sample Size Sensitivity

Figure 3 shows sensitivity of the required sample size to the true response rate for the DTG + 3TC arm assuming a **2**% failure rate in the current ART non-switch arm and a 4% margin.

Figure 3 Sample size sensitivity for the Snapshot Virologic Failure



Power=90%, NI margin=4%, control arm failure rate=2% N=**275** per arm, NI margin=4%, control arm failure rate=**2**%

Section 9.3.2 Analysis Data Sets

Previous text:

~~A last observation carried forward (LOCF) dataset, in which missing values will be carried forward from previous (non-missing) value during the treatment~~

~~**assessments, might be used in the analysis of health outcomes data.**~~ Further details will be provided in the RAP.

Current text:

Further details will be provided in the RAP.

Section 9.4.1. Efficacy Analyses

Previous text:

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.

Current text:

For the primary comparison, adjusted estimates of the difference in the rate of **virologic failures** between the two arms will be presented along with CIs based on a stratified analysis using Cochran-Mantel-Haenszel (CMH) weights.

Previous text:

Changes from baseline in CD4+ lymphocyte count and resistance data will be summarized overall and by baseline third agent class.

Current text:

Changes from baseline in CD4+ lymphocyte count **and in CD4+/CD8+ lymphocyte counts ratio** and resistance data will be summarized overall and by baseline third agent class.

Section 9.4.2. Safety Analyses

Previous text:

Statistical analysis of selected biomarkers and fasting lipids may be performed overall and by subgroup. Change from baseline in renal and bone biomarkers will be summarized by treatment and visit. Further details will be detailed in the RAP.

Current text:

Statistical analysis of selected biomarkers and fasting lipids may be performed overall and by subgroup. Change from baseline in renal, **inflammation** and bone biomarkers will be summarized by treatment and visit. **Change from baseline in Telomerase function will be summarized by treatment and visit.** Further details will be detailed in the RAP.

Section 10.6. Records Retention:

Previous text:

~~**ViiV/GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, ViiV/GSK standards/procedures, and/or institutional requirements.**~~

Current text:

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, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor.

Section 11. References

Previous text:

None

Current text:
Libre JM, Hung C-C, Brinson C, et. al. Phase III SWORD 1&2: Switch to DTG+RPV maintains virologic suppression through 48 wks. 2017 CROI, Seattle. Abstract 44LB.

Section 12.2.1.4. Proteinuria:

Previous 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.

Current text:

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 **and protein/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.

13.11.4. Protocol changes for Amendment 04 (2017-DEC-07) from Amendment 03 (2017-AUG-24): A global amendment applicable to all participating countries

Summary of Key Changes in Protocol Amendment 04 and Rationale

- Addition of a pharmacokinetics (PK) sub-study with sparse PK sampling and intensive PK sampling in a subset of subject in the DTG/3TC FDC arm to assess the PK parameters of DTG and 3TC of the DTG/3TC FDC in HIV-1 infected individuals as exploratory endpoints. This addition is based on Preliminary results of the pivotal bioequivalence study (204994) comparing the DTG/3TC FDC compared to the single entity tablets.

- Deletion of the secondary objective and endpoint assessing the safety and tolerability of DTG + 3TC once daily in those with creatinine clearance of between 30 – 49 mL/min/1.73m^2 compared to those with creatinine clearance of ≥ 50 mL/min/1.73m^2 because the exclusion criterion 18 has been updated to the higher threshold of creatinine clearance of ≥ 50 mL/min/1.73m^2.

- Inclusion of additional biomarkers for collection and analysis.

- Change of exclusion criterion 18 to a threshold of creatinine clearance of ≥ 50 mL/min/1.73m^2 based on the approved 3TC prescribing information at the time of this amendment. The rational and corresponding references for lowering this threshold were deleted as no longer relevant.

- Correction of the Time and event table footnote for plasma for storage samples to confirm the collection of these samples at the Screening visit; this was an error in the table.

- Correction of the rational for not making adjustment for multiplicity because of an error in the original text.

- Because of the addition of the PK substudy as Section 11, prior Section numbers from number 11 have been update by an increment of 1.

- For clarification purposes, the AE severity gradings in Appendix 8, Section 13.8.6 (Evaluating AEs and SAEs) were updated to be consistent with Appendix 9, Section 13.9. (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.

- Text was edited in Appendix 10, Section 13.10.2. to clarify wording for the country specific requirement for Japan.

List of Specific Changes: Unless stated otherwise, new text is represented in bold font, and deleted text in strikethrough font.

Title Page. Authors

Previous text:

PPD

Current text:

PPD

Section 1. Objective(s)/Endpoints and Section3. Objective(s)/Endpoints:

Previous text:

Objective	Endpoint
Secondary	
To evaluate the safety and tolerability of DTG + 3TC once daily in those with creatinine clearance of between 30 – 49 mL/min/1.73m^2 compared to those with creatinine clearance of ≥ 50 mL/min/1.73m^2	• Incidence and severity of AEs and laboratory abnormalities through 24 and 48 weeks • Proportion of subjects who discontinue treatment due to AEs through 24 and 48 weeks

Current text:

Objective	Endpoint
Secondary	
~~To evaluate the safety and tolerability of DTG + 3TC once daily in those with creatinine clearance of between 30 – 49 mL/min/1.73m^2 compared to those with creatinine clearance of ≥ 50 mL/min/1.73m^2~~	~~• Incidence and severity of AEs and laboratory abnormalities through 24 and 48 weeks~~ ~~• Proportion of subjects who discontinue treatment due to AEs through 24 and 48 weeks~~

Section 1. Overall Design and Section 4.1 Overall Design:

Previous text:

None.

Current text:

A pharmacokinetic (PK) substudy in the DTG+3TC arm will be conducted to evaluate DTG and 3TC concentrations using a sparse PK sampling approach at designated visits (See Section 11). In addition, intensive PK samples will be collected from a subgroup of subjects (approximately 30) enrolled at selected sites with the capability to perform intensive PK sampling.

Section3. Objective(s)/Endpoints:

Previous text:

None:

Current text:

Exploratory	
To assess the steady-state DTG and 3TC exposure in HIV-1 infected patients	**Steady state plasma PK parameters of DTG and 3TC will be assessed using intensive PK collected at week 4.**
To characterize the DTG and 3TC steady-state PK of the DTG/3TC FDC in HIV-1 infected patients	**Population estimates of DTG and 3TC PK parameters (e.g. apparent clearance [CL/F], apparent volume of distribution [V/F]) using DTG and 3TC intensive and sparse plasma concentrations at Weeks, 4, 8, 12, 24, 36 and 48**

Section3. Objective(s)/Endpoints:

Previous text:

Exploratory	
To evaluate the effect of patient characteristics (e.g., demographic factors, Baseline CD4) on antiviral and immunological responses to DTG + 3TC compared to TBR	• Proportion of subjects by subgroup(s) (e.g., by age, gender, Baseline CD4) with snapshot virologic failure at Weeks 24 and 48 • Change from Baseline in CD4+ cell counts at Weeks 24 and 48 by patient subgroups
To asses willingness to switch for subjects treated with DTG + 3TC compared to TBR	Reasons for Willingness to Switch at Day 1
To evaluate biomarkers of telomerase function in a subset of subjects treated with DTG + 3TC compared to TBR.	Change from baseline in biomarkers of telomerase function at Weeks 48 and 96
To evaluate inflammation biomarkers in a subset of subjects treated with DTG+ 3TC compared to TBR	Change from Baseline in inflammation biomarkers at Weeks 48

To evaluate the longer term antiviral and immunological effects, safety and tolerability of DTG + 3TC once daily in subjects treated with DTG + 3TC since the Early Switch Phase	For subjects in the DTG + 3TC arm since Early Switch Phase: • Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 96 using the Snapshot algorithm for the ITT-E population • Change from Baseline in CD4+ lymphocyte count and in CD4+/CD8+ cell count ratio at Week 96 • Incidence and severity of AEs and laboratory abnormalities over 96 weeks • Proportion of subjects who discontinue treatment due to AEs over 96 weeks • Incidence of disease progression (HIV associated conditions, AIDS and death) through Week 96 • Change from Baseline in renal and bone biomarkers at Week 96 • Change from baseline in biomarkers of inflammation and telomerase function at week 96
To evaluate the antiviral and immunological effects, safety and tolerability of DTG + 3TC for subjects switching in the Late Switch Phase	For subjects switching to DTG + 3TC in the Late Switch Phase: • Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 96 using the Snapshot algorithm for the ITT-E population • Change from Baseline in CD4+ lymphocyte count and in CD4+/CD8+ cell count ratio at Week 96 • Incidence and severity of AEs and laboratory abnormalities during the Late Switch Phase • Proportion of subjects who discontinue treatment due to AEs during the Late Switch Phase • Incidence of disease progression (HIV associated conditions, AIDS and death) during the Late Switch Phase • Change from Baseline in renal and bone biomarkers at Week 96 • Change from baseline in biomarkers of inflammation and telomerase function at week 96

Current text:

Exploratory	
To evaluate the effect of patient characteristics (e.g., demographic factors, Baseline CD4) on antiviral and immunological responses to DTG + 3TC compared to TBR	• Proportion of subjects by subgroup(s) (e.g., by age, gender, Baseline CD4) with snapshot virologic failure at Weeks 24 and 48 • Change from Baseline in CD4+ cell counts at Weeks 24 and 48 by patient subgroups
To asses willingness to switch for subjects treated with DTG + 3TC compared to TBR	Reasons for Willingness to Switch at Day 1
To evaluate biomarkers of telomerase function in a subset of subjects treated with DTG + 3TC compared to TBR.	Change from baseline in biomarkers of telomerase function at Weeks 48 and 96
To evaluate inflammation biomarkers **and insulin resistance** in a subset of subjects treated with DTG+ 3TC compared to TBR	Change from Baseline in inflammation biomarkers **and homeostasis model of assessment-insulin resistance (HOMA-IR)** at Weeks 48
To evaluate the longer term antiviral and immunological effects, safety and tolerability of DTG + 3TC once daily in subjects treated with DTG + 3TC since the Early Switch Phase	For subjects in the DTG + 3TC arm since Early Switch Phase: • Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 96 using the Snapshot algorithm for the ITT-E population • Change from Baseline in CD4+ lymphocyte count and in CD4+/CD8+ cell count ratio at Week 96 • Incidence and severity of AEs and laboratory abnormalities over 96 weeks • Proportion of subjects who discontinue treatment due to AEs over 96 weeks • Incidence of disease progression (HIV associated conditions, AIDS and death) through Week 96 • Change from Baseline in renal and bone biomarkers at Week 96 • Change from baseline in biomarkers of inflammation, **HOMA-IR** and telomerase function at week 96
To evaluate the antiviral and immunological effects, safety and tolerability of DTG + 3TC for subjects switching in the Late Switch Phase	For subjects switching to DTG + 3TC in the Late Switch Phase: • Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 96 using the Snapshot algorithm for the ITT-E population • Change from Baseline in CD4+ lymphocyte count and in CD4+/CD8+ cell count ratio at Week 96 • Incidence and severity of AEs and

	laboratory abnormalities during the Late Switch Phase • Proportion of subjects who discontinue treatment due to AEs during the Late Switch Phase • Incidence of disease progression (HIV associated conditions, AIDS and death) during the Late Switch Phase • Change from Baseline in renal and bone biomarkers at Week 96 • Change from baseline in biomarkers of inflammation, **HOMA-IR** and telomerase function at week 96

Section 4.2.4 Continuation Phase (Post Week 100)

Previous text:

Assessments during the Continuation Phase are limited and will consist of safety laboratory assessments, including CD4+ lymphocyte counts that would be considered part of standard of care therapy for HIV-infected individuals.

Current text:

Assessments during the Continuation Phase are limited and will **include plasma HIV-1 RNA and collection of AEs and SAEs.** ~~consist of safety laboratory assessments, including CD4+ lymphocyte counts that would be considered part of standard of care therapy for HIV-infected individuals.~~

Section 4.4 Design Justification:

Previous text:

This study also will evaluate the safety and tolerability of this 2-drug regimen in persons with a creatinine clearance of between 30 – 49 mL/min/1.73m^2. The DTG 50mg dose is approved for persons with a creatinine clearance of as low as 30 mL/min/1.73m^2. 3TC plasma concentrations area under the curve (AUC) are increased in patients with moderate to severe renal impairment due to decreased clearance, and the current label recommends halving the dose to 150 mg once a day for a creatinine clearance of between 30 – 49 mL/min/1.73m^2. However, several randomized controlled studies that have compared a total 3TC daily dose of 600 mg/day to 300 mg/day showed only small, statistically non-significant differences between the treatment arms in the frequency of AEs, drug-related AEs, SAEs, Grade 3/4 clinical and laboratory toxicities and withdrawals due to AEs [Eron, 1995; GlaxoWellcome Document Number UCR/95/003, 1995; GlaxoWellcome Document Number GIO/94/005, 1995]. Our study will allow inclusion of HIV-infected persons with creatinine clearance of ≥30 mL/min/1.73m^2 to confirm these earlier observations.

Current text:

~~**This study also will evaluate the safety and tolerability of this 2-drug regimen in persons with a creatinine clearance of between 30 – 49 mL/min/1.73m^2. The DTG 50mg dose is approved for persons with a creatinine clearance of as low as 30 mL/min/1.73m^2. 3TC plasma concentrations area under the curve (AUC) are increased in patients with moderate to severe renal impairment due to decreased clearance, and the current label recommends halving the dose to 150 mg once a day for a creatinine clearance of between 30 – 49 mL/min/1.73m^2. However, several randomized controlled studies that have compared a total 3TC daily dose of 600 mg/day to 300 mg/day showed only small, statistically non-significant differences between the treatment arms in the frequency of AEs, drug-related AEs, SAEs, Grade 3/4 clinical and laboratory toxicities and withdrawals due to AEs [Eron, 1995; GlaxoWellcome Document Number UCR/95/003, 1995; GlaxoWellcome, Document Number GIO/94/005, 1995]. Our study will allow inclusion of HIV-infected persons with creatinine clearance of ≥30 mL/min/1.73m^2 to confirm these earlier observations.**~~

Section 4.5 Dose Justification:

Previous text:

None.

Current text:

Based on the preliminary results of the pivotal bioequivalence study (204994), a bilayer tablet formulation with a core which utilizes the same formulation in the respective layers as the single entity tablets was selected. When administered in the fasted state, the bilayer tablet demonstrated bioequivalence to the single entity tablets for dolutegravir area under the curve zero to infinity (AUC(0-∞)) & maximum concentration (Cmax) and lamivudine AUC(0-∞). However, the bilayer tablet showed a modest increase in lamivudine Cmax compared to the single entity tablet, which is not considered to be clinically significant. PK of the FDC components will be evaluated using a combination of intensive and sparse sampling.

Section 4.6.1 Risk Assessment:

Previous text:

DTG and 3TC: Renal function	**DTG**: Mild elevations of creatinine have been observed with DTG which are related to a likely benign effect on creatinine secretion with blockade of OCT-2. DTG has been shown to have no significant effect on glomerular filtration rate (GFR) or effective renal plasma flow. **3TC**: 3TC is eliminated by renal excretion and exposures increase in patients with	Specific/detailed toxicity management guidance is provided for subjects who develop a decline in renal function (Section12.2.1.3). Creatinine clearance 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.

	renal dysfunction. 3TC is not recommended to treat patients with a creatinine clearance <50 mL/min.	Subjects with creatinine clearance <30 mL/min are excluded from participation in this study. Safety events, including laboratory toxicities will be monitored closely in subjects with creatinine clearance between 30-49 mL/min, as outlined in the Time and Events table.

Current text:

DTG and 3TC: Renal function	**DTG**: Mild elevations of creatinine have been observed with DTG which are related to a likely benign effect on creatinine secretion with blockade of OCT-2. DTG has been shown to have no significant effect on glomerular filtration rate (GFR) or effective renal plasma flow. **3TC**: 3TC is eliminated by renal excretion and exposures increase in patients with renal dysfunction. ~~3TC is not recommended to treat patients with a creatinine clearance <50 mL/min.~~	Specific/detailed toxicity management guidance is provided for subjects who develop a decline in renal function (Section**13.**2.1.3). Creatinine clearance 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. Subjects with creatinine clearance **<50** mL/min are excluded from participation in this study. ~~Safety events, including laboratory toxicities will be monitored closely in subjects with creatinine clearance between 30-49 mL/min, as outlined in the Time and Events table.~~

Section 5.1 Inclusion Criteria, clarification of criterion 1:

Inclusion criterion 1:

Previous text:

Aged 18 years or older (or ≥18 where required by local regulatory agencies), at the time of signing the informed consent

Current text:

Aged 18 years or older (or ~~≥18~~ **older** where required by local regulatory agencies), at the time of signing the informed consent

Section 5.2 Exclusion Criteria, update of exclusion criterion 18:

Exclusion criterion 18:

Previous text:

Creatinine clearance of <30 mL/min/1.73m^2 via CKD-EPI method

Current text

Creatinine clearance of <~~3~~50 mL/min/1.73m^2 via CKD-EPI method

Section 6.1 Investigational Product and Other Study Treatment

Previous text:

	Study Treatment (Open Label Randomised Phase, Day 1 to Week 100)
Product name:	**DTG + 3TC FDC**
Formulation description:	Clinical Trial Material
Dosage form:	Tablet
Unit dose strength(s)/Dosage level(s):	50mg/300mg
Route of Administration:	Oral
Dosing instructions:	Take one tablet daily.
Physical description:	White, oval, film-coated tablets. The tablets are packed in high density polyethylene (HDPE) bottles with induction seals, and child-resistant closures. Each 60mL bottle contains 30 tablets.

Current text:

	Study Treatment (Open Label Randomised Phase, Day 1 to Week 100)
Product name:	**DTG + 3TC FDC**
Formulation description:	Clinical Trial Material
Dosage form:	Tablet
Unit dose strength(s)/Dosage level(s):	50mg/300mg
Route of Administration:	Oral
Dosing instructions:	Take one tablet daily.
Physical description:	White, oval, film-coated tablets **with 'SV 137' debossed on one face**. The tablets are packed in high density polyethylene (HDPE) bottles with induction seals, **2gm desiccant**, and child-resistant closures. Each 60mL bottle contains 30 tablets.

Section 7.1. Time and Event Table:

Addition of insulin and HbA1c to biomarkers

Previous text:

Renal and bone marker analytes (blood/urine)[v]

Current text:

Insulin, HbA1c, renal and bone marker analytes (blood/urine)[v]

Section 7.1. Time and Event Table:

Correction of Footnote o:

Previous text:

Plasma samples for storage will be collected at each visit starting at Day 1, including unscheduled visits (e.g. for HIV-1 RNA levels and immunological parameters). These samples will be used when needed such as when samples are lost, arrive at the laboratory unevaluable, or for genotypic and/or phenotypic analyses when subjects meet Suspected and Confirmed Virologic Withdrawal criteria.

Current text:

Plasma samples for storage will be collected at each visit starting at ~~Day 1~~ **Screening,** including unscheduled visits (e.g. for HIV-1 RNA levels and immunological parameters). These samples will be used when needed such as when samples are lost, arrive at the laboratory unevaluable, or for genotypic and/or phenotypic analyses when subjects meet Suspected and Confirmed Virologic Withdrawal criteria.

Addition to Footnote v:

Previous text:

Blood sample for renal and bone biomarker assessments

Current text:

Blood sample for **insulin, Hb1Ac,** renal and bone biomarker assessments

PK assessments:

Previous text:

None

Current text:

Procedures	Screening Visit[a]	Open-label Randomised Phase												Continuation Phase[c]	Withdrawal	Follow-up[d]
		Week														
		Baseline / Day 1	4	8	12	24	36	48	52 Switch Visit[b]	60	72	84	96	100	Every 12 weeks after Week 100	
Pharmacokinetic[cc]																
Intensive PK sample collection at selected sites for subset of ~30 subjects (Fasting)[cc]			X[dd]													
Dispense PK diary Card to intensive PK sub-set		X														
Sparse PK sample collection[cc]			X[ee]	X	X	X	X	X								
Dispense PK Diary Card to Sparse PK subjects		X	X	X	X	X	X									

Additional footnotes:

cc:PK sampling in subjects from the DTG/3TC FDC arm only, as detailed in Section 11.

dd: Intensive PK sampling in a subset of subjects from the DTG/3TC FDC arm at select sites at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 10 and 24 hours post-dose. On the intensive PK day, patients are required to fast from 8 hours prior to dosing and then through 4 hours post-dose. Detailed in Section 11.

ee: At Week 4, subjects who performed intensive PK do not perform Sparse PK sampling.

Section 7.4.6 Clinical Safety Laboratory Assessments

Addition to Table 1 of Protocol Required Safety Laboratory Assessments

Previous text:

None

Current text:

HbA1c, Insulin, HOMA-IR
Addition to Table 1 footnote: **HbA1c = glycated haemoglobin, HOMA-IR = homeostasis model of assessment – insulin resistance**

Section 7.5 Biomarkers

HbA1c, insulin, HOMA-IR, and D-dimer were added to the list of biomarkers.

Previous text:

Blood is being collected to perform assessments of biomarkers of inflammation and telomere function.

Current text:

Blood is being collected to perform assessments of biomarkers of **insulin resistance**, inflammation and telomere function.

Insulin, HbA1c, and HOMA-IR

Additional Section 7.8. Pharmacokinetic Assessments:

Previous text:

None

Current text:

A PK substudy will be performed (see Section 11 for details).

Section 9.3.4. Interim Analysis:

Previous text:

Further data cuts and analyses may be conducted as necessary 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 analyses will be secondary.

Current text:

Further data cuts and analyses may be conducted as necessary 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 analyses will be secondary.

Additional Section 9.4.5. Pharmacokinetic Analysis:

Previous text:

None

Current text:

See Section 11 for details.

Additional Section 11. PHARMACOKINETIC SUBSTUDY:

Previous text:

None.

Current text:

11. PHARMACOKINETIC SUBSTUDY

11.1.1. Rationale for Pharmacokinetic Evaluation

Preliminary results of the pivotal bioequivalence study (204994) showed that when administered in the fasted state, the bilayer tablet demonstrated bioequivalence to the single entity tablets for dolutegravir AUC(0-∞) & Cmax and lamivudine AUC(0-∞). However, the bilayer tablet showed a modest increase in lamivudine Cmax compared to the single entity tablet, which is not considered to be clinically significant. PK of the FDC components will be evaluated using a combination of intensive and sparse sampling.

11.1.2. Exploratory Objectives

- **To assess the steady-state DTG and 3TC exposure in HIV-1 infected patients.**
- **To characterize the DTG and 3TC steady-state PK of the DTG/3TC FDC in HIV-1 infected patients.**

11.1.3. Exploratory Endpoints

- **Steady state plasma PK parameters of DTG and 3TC will be assessed using intensive PK collected at week 4.**
- **Population estimates of PK parameters (e.g. apparent clearance [CL/F], apparent volume of distribution [V/F]) using DTG and 3TC intensive and sparse plasma concentrations at Weeks, 4, 8, 12, 24, 36 and 48.**

11.1.4. Pharmacokinetic Sample Collection

For each timepoint two separate blood samples will be collected into di-potassium ethylenediaminetetraacetic acid (K2EDTA) tubes. Table 3 and Table 4 list the

sampling schedule to be followed for the assessment of intensive and sparse PK, respectively. The sub-set of subjects undergoing intensive PK sampling at selected sites will not undergo Sparse PK sampling at Week4, however, these subjects will undergo Sparse PK sampling at other PK visits (Table 3 and Table 4).

Table 3 Intensive Pharmacokinetic Sampling Schedule in a Subset of Subjects

Study visit	Sample Times Relative to Dose
Week 4	Pre-dose[a], 0.5, 1, 1.5, 2, 3, 4, 6, 10 and 24[b] hours post-dose

a. Pre-dose samples will be collected 20-28 hours after the prior dose AND approximately 15 minutes before the morning dose which will be taken under observation at the clinic.
b. Subjects in the intensive PK sampling group must return to the site the next morning immediately following the Week 4 visit for the 24 hour post-dose blood sample collection.

Table 4 Sparse Pharmacokinetic Sampling Schedule

Study Visit	PK sample collection time relative to dose	PK Sampling Group
Week 4	1 pre-dose[a,b] sample AND 1 sample 1 hour post-dose[b]	All subjects[e] except for subjects participating in the intensive PK group
Week 8	1 sample 1 to 4 hours post-dose[c]	All subjects[e]
Week 12	1 sample 4 to 12 hours post-dose[d]	
Weeks 24, 36 and 48	1 pre-dose sample[a]	

a. Pre-dose samples will be collected 20-28 hours after the prior dose AND approximately 15 minutes before the morning dose which will be taken under observation at the clinic.
b. Both sample timepoints must be obtained from each subject
c. The 1 to 4 hours sample may be drawn any time between 1 – 4 hours post-dose
d. The 4 to 12 hours sample may be drawn any time between 4 – 12 hours post-dose
e. All subjects are expected to participate in sparse PK

To allow flexibility in scheduling PK draws while maintaining quality and accuracy, the week 8 and week 12 samples can be drawn interchangeably (i.e. 1 to 4 hours post-dose drawn at week 12 and the 4 to 12 hours post-dose drawn at week 8) as long as both the 1 to 4 hours post-dose and 4 to 12 hours post-dose samples are obtained for each subject. In addition, flexibility is allowed in collecting the post-dose sample anywhere from 1 to 4 hours and 4 to 12 hours so that a range of sample time can be obtained. To achieve this, the subject may choose to remain in clinic until at least 1 hour after taking the DTG dose and may choose to return to the clinic 4 to 12 hours after taking the medication.

It is important to collect PK samples according to the following procedures:

• To enhance the quality of the data, subjects undergoing intensive and/or sparse PK assessments will be asked to complete a diary card with the following information which will be included in eCRF:

o The date and time of the DTG/3TC FDC administration for 3 days prior to the scheduled PK clinic visit;

o Whether or not the doses were taken with a meal

o Whether or not the subject vomited within 4 hours of taking the study drug

In addition the following information should be recorded in the eCRF:

o The actual date and time of the observed dose taken at the clinic visit;

o The actual date and time of the PK samples collected

• For the 3 days in advance of a PK clinic visit, the subject must be instructed to take the DTG/3TC FDC without regard to food at a time that corresponds with the scheduled PK visit time to allow for a pre-dose sample collection as close to 24 hour after the previous dose.

• On the days of the either intensive PK or sparse pre-dose sample collection, the subjects should not take a dose of the DTG/3TC FDC until instructed at the clinic visit.

• The subjects participating in intensive PK sampling will be requested to present at the clinic fasted for at least 8 hours at the week 4 visit. These subjects should return to the clinic next day for the 24 hours post-dose sample collection, prior to taking a DTG/3TC FDC dose. The 24 hours post-dose sample may be collected without regard to food.

• The sparse PK samples will be collected without regard to food (however the fed/fasted status information will be collected and recorded on the eCRF)

Note: If a subject presents at the clinic for pre-dose PK sample collection having already taken the daily dose or having missed doses within the previous 3 days, it is recommended to reschedule PK sampling as early as possible within the defined PK visit window. It is recommended not to collect PK samples if date and time of dosing for the previous 3 days cannot reliably be confirmed. If PK cannot be rescheduled within the pre-defined visit of interest window (specified in the study procedure manual), no PK sample is to be collected for that visit.

11.1.5. Bioanalysis of DTG and 3TC Samples

The bioanalysis of plasma DTG and 3TC samples will be performed by PPD using GSK validated LC/MS/MS assay.

11.1.6. Pharmacokinetic Populations

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

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

The defining of evaluable drug concentrations and further details on the PK populations will be described in the RAP.

11.1.7. Pharmacokinetic Analyses

The following intensive PK parameters will be summarized for 3TC and DTG: maximum observed plasma concentration (Cmax); time to maximum observed plasma concentration (tmax); observed plasma concentration at the end of a dosing interval (Ctau); observed pre-dose plasma concentration (C0); area under the concentration-time curve in one dosing interval (AUC(0-τ)).

11.1.8. Population PK

If data permits, the sparse PK data will be pooled with the intensive PK data and potentially data from other studies to perform integrated PK analyses for DTG and 3TC to estimate steady-state AUC, Cmax and Cτ for individual subjects. Further details of the PK analyses will be provided in the RAP. The population PK analyses may be reported separately.

Section 12. REFERENCES:

Previous text:

Dolutegravir (Tivicay) Product Insert. Available at: http://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Tivicay/pdf/TIVICAY-PI-PIL.PDF. June 2016. Accessed February 8, 2017.

Epivir/Lamivudine Product Insert. Available at: http://www.viivhealthcare.com/media/32160/us_epivir.pdf. January, 2013. Accessed February 8, 2017.

GlaxoWellcome Document Number: GIO/94/005. A Randomized, Controlled Lamivudine (3TC) Double-blind Trial to Compare the Safety and Efficacy of Zidovudine (ZDV) Monotherapy versus Lamivudine Plus ZDV in Combination in Treating HIV-1 Infected Patients Who Are ZDV Therapy with a CD4 Cell Counts between 100-400 cells/mm^3 (Protocol No: NUCB3002). May 18, 1995.

GlaxoWellcome Document Number: UCR/95/003. A Randomized 3TC, ddC Double-blind (ZDV Open-labeled) Multicenter Trial to Evaluate the Safety and Efficacy of 3TC

(low dose) Administered Concurrently with Zidovudine (ZDV) Versus 3TC (high dose) Administered Concurrently with ZDV Versus Dideoxycytidine (ddC) Administered Concurrently with ZDV in the Treatment of HIV-1 Infected ZDV-experienced (~24 Weeks) Patients with CD4 Cell Counts of 100-300/mm^3 (Protocol No: NUCA3002). May 17, 1995.

Current text:

Dolutegravir (Tivicay) Product Information. November 2017.

Epivir (Lamivudine) Product Information. September 2017.

~~GlaxoWellcome Document Number: GIO/94/005. A Randomized, Controlled Lamivudine (3TC) Double-blind Trial to Compare the Safety and Efficacy of Zidovudine (ZDV) Monotherapy versus Lamivudine Plus ZDV in Combination in Treating HIV-1 Infected Patients Who Are ZDV Therapy with a CD4 Cell Counts between 100-400 cells/mm^3 (Protocol No: NUCB3002). May 18, 1995.~~

~~GlaxoWellcome Document Number: UCR/95/003. A Randomized 3TC, ddC Double-blind (ZDV Open-labeled) Multicenter Trial to Evaluate the Safety and Efficacy of 3TC (low dose) Administered Concurrently with Zidovudine (ZDV) Versus 3TC (high dose) Administered Concurrently with ZDV Versus Dideoxycytidine (ddC) Administered Concurrently with ZDV in the Treatment of HIV-1 Infected ZDV-experienced (~24 Weeks) Patients with CD4 Cell Counts of 100-300/mm^3 (Protocol No: NUCA3002). May 17, 1995.~~

Section 13.2.1.5. Allergic Reaction

Previous text:

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.

Current text:

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.

Section 13.8.6. Evaluating AEs and SAEs

Previous text:

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 utilized 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.

Current 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 categories **in the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE Grading Table") in Section 13.9:**

- ~~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 utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.~~
- **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.

Section 13.10.2. Japan:

Previous text:

All drug will be provided centrally. For subjects receiving Descovy as their TBR in Japan, the baseline third agent must be DTG.

Current text:

All drug will be provided centrally. ~~For subjects~~ **In Japan, only subjects** receiving Descovy +**DTG** as their TBR ~~in Japan, the baseline third agent must be DTG~~ **are eligible for the study.**

13.11.5. Protocol changes for Amendment 05 (14-JUN-2018) from Amendment 04 (2017-DEC-07): A global amendment applicable to all participating countries

Summary of Key Changes in Protocol Amendment 05 and Rationale

Changes were made to the protocol to manage and mitigate risks following identification of a potential safety issue related to neural tube defects in infants born to women with exposure to dolutegravir at the time of conception. Changes were also made to include updated text to address a higher number of participants screened than planned, to update references to the DTG IB to reflect the most current versions and to add clarification and correct minor typos.

- The Risk Assessment table (Section 4.6.1) was updated to include language regarding risk and mitigation of neural tube defects.
- The withdrawal criteria (Section 5.4) were updated to include a reminder that females of reproductive potential who change their minds and desire to be pregnant, or who state they no longer are willing to comply with the approved pregnancy avoidance methods, should also be withdrawn from the study.
- The Time and Events table (Section 7.1). was updated to include a reminder for investigators to check at every visit that females of reproductive potential are avoiding pregnancy.
- The modified list of highly effective methods for avoiding pregnancy in FRP (Section 13.3.1) was updated to exclude the double barrier method of contraception, which does not meet updated GSK/ViiV criteria for a highly effective method.
- The Type and Number of Subjects (Section 4.3) and Sample Size Assumptions (Section 9.2.1) were updated to address a higher number of participants screened than planned.

List of Specific Changes. Unless stated otherwise, new text is represented in bold font, and deleted text in strikethrough font.

Title Page. Authors:

Previous text:

PPD

PPD

Current text:

PPD

Protocol Synopsis for Study 204862, Type and Number of Subjects:

Added the following text: **The study closed screening on 18 May 2018 with a total of 933 screened subjects and based on current randomisation numbers and current screen failure rate a total of approximately 750 subjects are expected to be randomised.**

Section 3 Objectives and Endpoints:

To evaluate inflammation biomarkers and insulin resistance in a subset of subjects treated with DTG+ 3TC compared to TBR	Change from Baseline in inflammation biomarkers and homeostasis model of assessment-insulin resistance (HOMA-IR) at Weeks 48 **and 96**

Section 4.3 Type and Number of Subjects:

Added the following text: **The study closed screening on 18 May 2018 with a total of 933 screened subjects and based on current randomisation numbers and current screen failure rate a total of approximately 750 subjects are expected to be randomised.**

Section 4.6.1 Risk Assessment:

Added the following text:

DTG: Neural tube defects	**In one ongoing birth outcome surveillance study in Botswana, early results from an unplanned interim analysis show that 4/426 (0.9%) of women who were taking DTG when they became pregnant had babies with neural tube defects compared to a background rate of 0.1%.**	**1. A female subject is eligible to participate if she is not pregnant, not lactating, and, if she is a female of reproductive potential, agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see**

		Appendix 3, Section 13.3.1) from 30 days prior to the first dose of study medication and for at least 2 weeks after the last dose of study medication. **2. Women who are breastfeeding or plan to become pregnant or breastfeed during the study are excluded.** **3. Women who become pregnant, or who desire to be pregnant while in the study, or who state they no longer are willing to comply with the approved pregnancy avoidance methods, will have study treatment discontinued and be withdrawn from the study.** **4. Females of reproductive potential are reminded re: pregnancy avoidance and adherence to contraception requirements at every study visit.** **5. Pregnancy status is monitored at every study visit.**

Section 5.1 Inclusion Criteria:

Updated inclusion criterion 6: *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 Section 13.3) from 30 days prior to the first dose of study medication **and for at least 2 weeks after the last dose of study medication**. ~~and until the last dose of study medication and completion of the follow-up visit.~~

Section 5.4 Withdrawal and Stopping Criteria:

Previous text:

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

Current text:

- Pregnancy (intrauterine), regardless of termination status of pregnancy. **(Section 7.4.2). As a reminder, females of reproductive potential who change their minds and desire to be pregnant, or who state they no longer are willing to comply with the approved pregnancy avoidance methods, should also be withdrawn from the study.**

Section 7.1 Time and Events Table:

Inserted footnote t: **Remind females of reproductive potential of the need to avoid pregnancy while in study and adherence to the study's contraception requirements.**

Due to the addition of this footnote, the sequence of footnotes has changed.

Section 7.3.1 Efficacy Evaluations:

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 Revised Classification System for HIV Infection in Adults (see Section 13.7). **When assessing CDC stage at screening consider only the latest available CD4 T-cell count, including CD4 T-cell count at screening. If a stage-3–defining opportunistic illness has been diagnosed up to screening, then the stage is 3 regardless of CD4 T-cell count test results.**

For Baseline CDC classification at Day 1 use latest CD4 T-cell count, including CD4 T-cell count at baseline. If a stage-3–defining opportunistic illness has been diagnosed between screening and Day 1, then the stage is 3 regardless of CD4 T-cell count test results.

Section 9.2.1 Sample Size Assumptions:

Previous text:

If we observed a 2% virologic failure rate for the non-switch subjects then non-inferiority would be declared if the observed treatment difference was less than or equal to ~~1.24~~ percentage points.

Current text:

If we observed a 2% virologic failure rate for the non-switch subjects then non-inferiority would be declared if the observed treatment difference was less than or equal to **1.3** percentage points.

Added the following text: **While the targeted study size was 550 randomised subjects (from a target of 800 screened subjects), the study was over-enrolled based on an unexpected surge in recruitment in the last week of screening. Based on an**

estimated screen failure rate of 20%, a total of 750 subjects are expected to be randomized.

In this case where 750 subjects are randomized, this will provide 97.5% power to show non-inferiority with the current assumptions, and non-inferiority can be declared if the actual observed treatment difference in the trial is less than or equal to 1.6%.

Section 12 References:

References to the DTG IB have been updated to add DTG IB version 11, supplement 01 and 02 as follows:

GlaxoSmithKline Document Number 2017N352880_00: GSK1349572 Clinical Investigator's Brochure, Version 11, Supplement 01, 11 December 2017.

GlaxoSmithKline Document Number 2017N352880_01: GSK1349572 Clinical Investigator's Brochure, Version 11, Supplement 02, June 2018.

In text references to the DTG IB were also updated to include the link for GSK Document Numbers for IB version 11, and version 11, supplement 01 and 02.

Section 13.3.1 Modified list of highly effective methods for avoiding pregnancy in females of reproductive potential (FRP) and Collection of Pregnancy Information:

Removed the following text: ~~Male condom combined with a vaginal spermicide (foam, gel, film, cream, or suppository) [Hatcher, 2007].~~

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

13.11.6. Protocol changes for Amendment 06 (29-AUG-2018) from Amendment 05 (14-JUN-2018)

Summary of Key Changes in Protocol Amendment 06 and Rationale

Changes were made to the protocol to update the study design to extend the Randomized Early Switch Phase through to 148 weeks instead of Week 52, delaying the late switch to Week 148 with long term follow-up through to completion of the study at Week 200. The rationale for this change is to collect and assess long-term comparative efficacy and safety data for DTG + 3TC FDC vs. a TAF-based regimen.

List of Specific Changes. Unless stated otherwise, new text is represented in bold font, and deleted text in strikethrough font.

Title Page. Authors:

Previous text:

PPD

Current text:

PPD

Medical Monitor/Sponsor Information Page

Previous text:

Sponsor Legal Registered Address:

ViiV Healthcare UK Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

Sponsor Contact Address:

ViiV Healthcare
Five Moore Drive
P.O. 13398
Research Triangle Park, NC 27709-3398, USA
Telephone: PPD

Current text:

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

US IND Sponsor Name and Legal Registered Address:

ViiV Healthcare
Five Moore Drive
P.O. 13398
Research Triangle Park, NC 27709-3398, USA
Telephone: PPD

Previous text:

This study is sponsored by ViiV Healthcare. GlaxoSmithKline is supporting ViiV Healthcare in the conduct of this study.

Current text:

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

Protocol Synopsis for Study 201862:

Previous text:

This study also will characterize the long-term antiviral activity, tolerability and safety of DTG + 3TC ~~through Week 100~~.

Current text:

This study also will characterize the long-term antiviral activity, tolerability and safety of DTG + 3TC **compared to TBR** through **Week 144 and characterize the long-term antiviral activity, tolerability and safety of DTG + 3TC through Week 200.**

Previous text:

Objective	Endpoint
Primary	
To demonstrate the non-inferior antiviral activity of switching to DTG +3TC once daily compared to continuation of TBR over 48 weeks in HIV-1 infected, ART therapy (ART)-experienced, virologically suppressed subjects	Virologic failure endpoint as per FDA snapshot category at Week 48
Secondary	
To demonstrate the antiviral activity of switching to DTG +3TC once daily compared to continuation of TBR over 48 weeks	Proportion of subjects with plasma HIV-1 RNA <50 copies c/mL at Week 48 using the Snapshot algorithm for the ITT-E population
To demonstrate the antiviral activity of switching to DTG + 3TC once daily compared to continuation of TBR over 24 weeks	• Virologic failure endpoint as per FDA snapshot category at Week 24 • Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 24 using the Snapshot algorithm for the ITT-E population

Objective	Endpoint
To evaluate the immune effects of DTG + 3TC once daily compared to continuation of TBR	• Change from Baseline in CD4+ cell count and in CD4+/CD8+ cell counts ratio at Weeks 24 ~~and~~ 48 • Incidence of disease progression (HIV-associated conditions, AIDS, and death) through Week~~s 24 and 48~~
To evaluate the safety and tolerability of DTG + 3TC once daily compared to TBR over time	• Incidence and severity of AEs and laboratory abnormalities through 24 ~~and~~ 48 weeks • ~~Cumulative incidence of AEs by time to first occurrence~~ • Proportion of subjects who discontinue treatment due to AEs through ~~24 and 48~~ weeks
To evaluate the effects of DTG + 3TC once daily on fasting lipids over time compared to TBR	Change from Baseline in fasting lipids at Weeks 24 ~~and~~ 48
To assess viral resistance in subjects meeting Virologic Withdrawal Criteria	Incidence of observed genotypic and phenotypic resistance to ARVs for subjects meeting Virologic Withdrawal Criteria
To evaluate renal (in urine and blood) and bone (in blood) biomarkers in subjects treated with DTG + 3TC compared to TBR	Change from Baseline in renal and bone biomarkers at Weeks 24 and 48
To assess health related quality of life for subjects treated with DTG + 3TC compared to TBR	Change from Baseline in health status using EQ-5D-5L at Weeks 24 ~~and~~ 48 (or Withdrawal from the study)

Current text:

Objective	Endpoint
Primary	
To demonstrate the non-inferior antiviral activity of switching to DTG +3TC once daily compared to continuation of TBR over 48 weeks in HIV-1 infected, ART therapy (ART)-experienced, virologically suppressed subjects	Virologic failure endpoint as per FDA snapshot category at Week 48
Secondary	
To demonstrate the antiviral activity of switching to DTG +3TC once daily compared to continuation of TBR over 48 weeks	Proportion of subjects with plasma HIV-1 RNA <50 copies c/mL at Week 48 using the Snapshot algorithm for the ITT-E population
To demonstrate the antiviral activity of switching to DTG + 3TC once daily compared to continuation of TBR over 24 weeks**, 96 weeks and 144 weeks**	• Virologic failure endpoint as per FDA snapshot category at Week**s** 24**, 96 and 144** • Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week**s** 24**, 96 and 144** using the Snapshot algorithm for the ITT-E population

Objective	Endpoint
To evaluate the immune effects of DTG + 3TC once daily compared to continuation of TBR **over 24, 48, 96 and 144 weeks**	• Change from Baseline in CD4+ cell count and in CD4+/CD8+ cell counts ratio at Weeks 24,48**, 96 and 144** • Incidence of disease progression (HIV-associated conditions, AIDS, and death) through Weeks 24, 48**, 96 and 144**
To evaluate the safety and tolerability of DTG + 3TC once daily compared to TBR over time	• Incidence and severity of AEs and laboratory abnormalities through **144** weeks • Proportion of subjects who discontinue treatment due to AEs through **144** weeks
To evaluate the effects of DTG + 3TC once daily on fasting lipids over time compared to TBR	Change from Baseline in fasting lipids at Weeks 24, 48**, 96 and 144**
To assess viral resistance in subjects meeting Virologic Withdrawal Criteria	Incidence of observed genotypic and phenotypic resistance to ARVs for subjects meeting Virologic Withdrawal Criteria
To evaluate renal (in urine and blood) and bone (in blood) biomarkers in subjects treated with DTG + 3TC compared to TBR	Change from Baseline in renal and bone biomarkers at Weeks 24, 48**, 96 and 144**
To assess health related quality of life for subjects treated with DTG + 3TC compared to TBR	Change from Baseline in health status using EQ-5D-5L at Weeks 24, 48**, 96 and 144** (or Withdrawal from the study)

Previous text:

This is a ~~100~~-week, Phase III, randomized, open-label, active-controlled, multicenter, parallel-group study to assess the non-inferior antiviral activity and safety of replacing a TBR with a two-drug regimen of DTG + 3TC in HIV-infected adults who are virologically suppressed and stable on a TBR. The study will include a Screening Phase (up to 28 days), a Randomized Early Switch Phase (Day 1 up to Week ~~52~~), a Randomized Late Switch Phase (Week ~~52~~ up to Week~~100~~), and a Continuation Phase (post Week ~~100~~). Approximately 550 HIV-1 infected adults who are on a stable TBR will be randomized 1:1 to switch to DTG + 3TC once daily (DTG + 3TC arm) for up to ~~100~~ weeks, or to continue their TBR for ~~52~~ weeks, at which time and if HIV1 RNA <50 c/mL at Week ~~48~~ (or upon retest by Week ~~52~~), these subjects will switch to DTG + 3TC up to Week ~~100~~. For subjects randomized to the TBR, provisions will be in place, as needed and after discussion with the study team, to assist patients in obtaining their TBR during the study.

The primary endpoint for the study is the proportion of participants who meet the Snapshot virologic failure criteria at Week 48 using the Intent-to-Treat Exposed (ITT-E) population. The Week 48 primary analysis will take place after the last subject has had their Week 48 viral load assessed, including any retests. Subjects randomized to DTG + 3TC will receive DTG + 3TC up to Week ~~100~~. Subjects randomized to TBR will have a Week ~~52~~ switch visit, allowing approximately 4 weeks for subjects who have a viral load

≥50 c/mL at Week ~~48~~ to have a retest prior to switch. The study will continue for at least ~~100~~ weeks.

Current text:

This is a **200**-week, Phase III, randomized, open-label, active-controlled, multicenter, parallel-group study to assess the non-inferior antiviral activity and safety of replacing a TBR with a two-drug regimen of DTG + 3TC in HIV-infected adults who are virologically suppressed and stable on a TBR. The study will include a Screening Phase (up to 28 days), a Randomized Early Switch Phase (Day 1 up to Week **148**), a Randomized Late Switch Phase **(Week 148 up to Week 200)** and a Continuation Phase (post Week **200**) **if DTG + 3TC fixed dose combination (FDC) is not yet approved and available locally.** Approximately 550 HIV-1 infected adults who are on a stable TBR will be randomized 1:1 to switch to DTG + 3TC once daily (DTG + 3TC arm) for up to **200** weeks, or to continue their TBR for **148** weeks, at which time and if HIV-1 RNA <50 c/mL at Week **144** (or upon retest by Week **148**), these subjects will switch to DTG + 3TC up to Week **200**. For subjects randomized to the TBR, provisions will be in place, as needed and after discussion with the study team, to assist patients in obtaining their TBR during the study. **For subjects who switch to DTG + 3TC at Week 148, a separate Late Switch Phase Time and Events Table is provided in Section 7.1.2 as these participants will be monitored closely for the first 24 weeks post-switch. Subjects who remain on DTG + 3TC will follow a separate Late Switch Phase Time and Events Table in Section 7.1.3.**

The primary endpoint for the study is the proportion of participants who meet the Snapshot virologic failure criteria at Week 48 using the Intent-to-Treat Exposed (ITT-E) population. The Week 48 primary analysis will take place after the last subject has had their Week 48 viral load assessed, including any retests. Subjects randomized to DTG + 3TC will receive DTG + 3TC up to Week **200.** Subjects randomized to TBR will have a Week **148** switch visit, allowing approximately 4 weeks for subjects who have a viral load ≥50 c/mL at Week **144** to have a retest prior to switch. The study will continue for at least **200** weeks.

Previous text:

The study will include a Screening Phase (up to 28 days), a Randomized Early Switch Phase (Day 1 up to Week ~~52~~), a Randomized Late Switch Phase (Week ~~52~~ up to Week ~~100~~) and a Continuation Phase (post Week ~~100~~). Subjects randomized to DTG + 3TC will receive DTG + 3TC up to Week ~~100~~. Subjects randomized to TBR will continue to take their current regimen up to Week ~~52~~, at which time and if HIV-1 RNA <50 c/mL at Week ~~48~~ (or upon retest by Week ~~52~~), these subjects will switch to DTG + 3TC up to Week ~~100~~. Randomization will be stratified by baseline third agent class (protease inhibitor [PI], integrase inhibitor [INI], or non-nucleoside reverse transcriptase inhibitor [NNRTI]).

The primary analysis at Week 48 will take place after the last subject completes 52 weeks on therapy, to allow for the collection of a confirmatory viral load measurement in subjects presenting with HIV-1 RNA ≥50 c/mL at the Week 48 visit. The secondary

analysis at Week 24 will take place after the last subject completes 28 weeks on therapy, to allow for the collection of a confirmatory viral load measurement in subjects presenting with HIV-1 RNA ≥50 c/mL at the Week 24 visit.

All subjects who successfully complete 100 weeks of treatment will ~~continue to have access to DTG + 3TC fixed-dose combination (FDC) in a Continuation Phase until:~~

- DTG ~~and~~ 3TC ~~are each~~ locally approved for use as ~~part of a dual~~ regimen, and ~~each of the single entities of DTG and 3TC are~~ available to subjects (e.g., through public health services or through their usual health insurance payer), or
- ~~the actual 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.

~~The purpose of the Continuation Phase is to ensure provision of DTG and 3TC.~~
Assessments during the Continuation Phase are limited.

Current text:

The study will include a Screening Phase (up to 28 days), a Randomized Early Switch Phase (Day 1 up to Week **148),** a Randomized Late Switch Phase (Week **148** up to Week **200**) and a Continuation Phase (post Week **2**00) **if DTG + 3TC FDC is not yet approved and available locally.** Subjects randomized to DTG + 3TC will receive DTG + 3TC up to Week **200**. Subjects randomized to TBR will continue to take their current regimen up to Week **144**, at which time and if HIV-1 RNA <50 c/mL at Week **144** (or upon retest by Week **148**), these subjects will switch to DTG + 3TC up to Week **200**. Randomization will be stratified by baseline third agent class (protease inhibitor [PI], integrase inhibitor [INI], or non-nucleoside reverse transcriptase inhibitor [NNRTI]).

The primary analysis at Week 48 will take place after the last subject completes **up to** 52 weeks on therapy, to allow for the collection of a confirmatory viral load measurement in subjects presenting with HIV-1 RNA ≥50 c/mL at the Week 48 visit. The secondary analysis at Week 24 will take place after the last subject completes **up to** 28 weeks on therapy, to allow for the collection of a confirmatory viral load measurement in subjects presenting with HIV-1 RNA ≥50 c/mL at the Week 24 visit. **Further secondary analyses will take place at Week 96, 144 and 196**.

All subjects who successfully complete **2**00 weeks of treatment will **complete the study and transition to locally approved and available DTG + 3TC fixed-dose combination (FDC) and be managed as per standard of care at their study site. Prior to completion of the Week 200 visit, sites will need to have confirmation that DTG + 3TC FDC is locally available for study subjects. If DTG + 3TC FDC is not yet approved and available locally, ViiV Healthcare will continue to provide study drug in a Continuation Phase until:**

- DTG + 3TC **FDC is** locally approved for use as **a 2-drug** regimen, and available to subjects (e.g., through public health services or through their usual health insurance payer), 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.

Assessments during the Continuation Phase are limited **and will include plasma HIV-1 RNA and collection of AEs/SAEs.**

Previous text:

The study closed screening on 18 May 2018 with a total of 933 screened subjects and ~~based on current randomisation numbers and current screen failure rate a total of approximately~~ 75~~0~~ subjects ~~are expected to be~~ randomised.

Current text:

The study closed screening on 18 May 2018 with a total of 933 screened subjects and **a total of** 7**43** subjects **were** randomised.

Section 2.1 Study Rationale:

Previous text: However, this longer life expectancy has been accompanied by higher rates of non-acquired immuno-deficiency syndrome (AIDS)-defining events (NADEs) such as cardiovascular disease, liver disease and cancer.

Current text: However, this longer life expectancy has been accompanied by higher rates of non-acquired immun**od**eficiency syndrome (AIDS)-defining events (NADEs) such as cardiovascular disease, liver disease and cancer.

Previous text:

Finally, if a 2-drug ART regimen is shown to be as effective and safe as conventional 3-drug regimens, the lower cost associated with taking one less drug for the lifetime of an HIV-infected person will have substantial individual and societal individual benefits.

The overall objective of the DTG + 3TC clinical development program is to develop a single tablet, fixed-dose, two-drug combination therapy regimen that ~~offers a high level of tolerability~~ and a high barrier to the emergence of viral resistance. A DTG + 3TC two-drug strategy may be effective in maintaining virologic suppression among treatment experienced subjects, while preserving future HIV-1 treatment options.

Study 204862 is being conducted to establish if human immunodeficiency virus type 1 (HIV-1) infected adult subjects with current virologic suppression on a TBR remain suppressed upon switching to a two-drug regimen with DTG + 3TC. ~~This study will provide important information regarding efficacy, safety, and health-related quality of life.~~ This trial is designed to demonstrate the non-inferior antiviral activity of switching

to DTG + 3TC once daily compared to continuation of a TBR over 48 weeks. This study will also characterize the long-term antiviral activity, tolerability and safety of DTG + 3TC through Week ~~100~~.

~~One of the potential risks of a 2-drug regimen is the increase in virologic failure associated with the emergence of drug resistance. DTG, with its higher barrier to resistance, may reduce the risk of treatment-emergent resistance in patients taking a 2-drug regimen. The pivotal Phase 3 studies of DTG in naïve subjects have shown the absence of treatment-emergent INI or NRTI resistance mutations through 144+ weeks of treatment [Walmsley, 2013]. The absence of treatment emergent mutations to DTG or background agents in ART-naïve individuals, the potency of both DTG and 3TC, and the well-tolerated safety profile of both drugs provides a strong rationale for the development of the DTG + 3TC STR as an important treatment option for patients.~~

Current text:

Finally, if a 2-drug ART regimen is shown to be as effective and safe as conventional 3-drug regimens, the lower cost associated with taking one less drug for the lifetime of an HIV-infected person will have substantial individual and societal individual benefits.

One of the potential risks of a 2-drug regimen is the increase in virologic failure associated with the emergence of drug resistance. DTG, with its higher barrier to resistance, may reduce the risk of treatment-emergent resistance in patients taking a 2-drug regimen. The pivotal Phase 3 studies of DTG in naïve subjects have shown the absence of treatment-emergent INI or NRTI resistance mutations through 144+ weeks of treatment [Walmsley, 2013]. The absence of treatment emergent mutations to DTG or background agents in ART-naïve individuals, the potency of both DTG and 3TC, and the well-tolerated safety profile of both drugs provides a strong rationale for the development of the DTG + 3TC STR as an important treatment option for patients.

The overall objective of the DTG + 3TC clinical development program is to develop a single tablet, fixed-dose, two-drug combination therapy regimen that **is as effective as 3-drug ART in treating HIV-1 infection**, is safe and well tolerated in the long-term, and **has** a high barrier to the emergence of viral resistance. A DTG + 3TC two-drug strategy may be effective in maintaining virologic suppression among treatment experienced subjects, while **improving long-term safety and tolerability, and** preserving future HIV-1 treatment options.

Study 204862 is being conducted to establish if human immunodeficiency virus type 1 (HIV-1) infected adult subjects with current virologic suppression on a TBR remain suppressed upon switching to a two-drug regimen with DTG + 3TC. This trial is designed to demonstrate the non-inferior antiviral activity of switching to DTG + 3TC once daily compared to continuation of a TBR over 48 weeks. **To better understand the long-term differences in antiviral efficacy, safety and tolerability between DTG + 3TC and TAF-based regimens, the comparative phase of the study will be extended to 148 weeks. The originally planned Week 52 Switch Visit in the TBR arm will be moved to Week 148 to allow for 2 additional years of comparative**

follow-up. This study will also characterize the long-term antiviral activity, tolerability and safety of DTG + 3TC through Week 200.

Previous text:

This study will also characterize the long-term antiviral activity, tolerability and safety of DTG + 3TC through Week ~~100~~.

Current text:

This study will also characterize the long-term antiviral activity, tolerability and safety of DTG + 3TC **compared to TBR** through Week **144 and the long-term antiviral activity, tolerability and safety of DTG + 3TC through Week 200.**

Section 2.2 Brief Background:

Added text: GEMINI-1 and GEMINI-2 are two identical global, double-blind, multicentre Phase III studies evaluating the efficacy and safety of DTG + 3TC once daily in treatment-naïve HIV-1-infected adults with Screening HIV-1 ≤500,000 c/mL. At 48 weeks, dual therapy with DTG + 3TC demonstrated non-inferior efficacy to DTG + TDF/FTC (in the primary endpoint: proportion of subjects with plasma HIV-1 RNA<50 c/ml by FDA Snapshot in the pooled ITT-E population [DTG/3TC n=716. DTG/TDF/FTC n= 717] 91% vs. 93% respectively, adjusted difference (95% CI) -1.7 (-4.4, 1.1). Across both studies, 6 participants on DTG + 3TC and 4 participants on DTG + TDF/FTC met protocol-defined virologic withdrawal criteria and none had treatment-emergent INSTI or NRTI resistance mutations. Overall, the rates of AEs were similar between arms, with low rates of withdrawals due to AEs for both arms [Cahn, 2018].

Section 3 Objectives and Endpoints:

Previous text:

Objective	Endpoint
Primary	
To demonstrate the non-inferior antiviral activity of switching to DTG +3TC once daily compared to continuation of TBR over 48 weeks in HIV-1 infected, ART therapy (ART)-experienced, virologically suppressed subjects	Virologic failure endpoint as per FDA snapshot category at Week 48
Secondary	
To demonstrate the antiviral activity of switching to DTG + 3TC once daily compared to continuation of TBR over 48 weeks	Proportion of subjects with plasma HIV-1 RNA <50 copies c/mL at Week 48 using the Snapshot algorithm for the ITT-E population
To demonstrate the antiviral activity of switching to DTG + 3TC once daily compared to continuation of TBR over 24 weeks	• Virologic failure endpoint as per FDA snapshot category at Week 24 • Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 24 using the Snapshot

Objective	Endpoint
	algorithm for the ITT-E population
To evaluate the immune effects of DTG + 3TC once daily compared to continuation of TBR	• Change from Baseline in CD4+ cell count and in CD4+/CD8+ cell count ratio at Weeks 24 ~~and~~ 48 • Incidence of disease progression (HIV-associated conditions, AIDS, and death) through Weeks 24 ~~and~~ 48
To evaluate the safety and tolerability of DTG + 3TC once daily compared to TBR over time	• Incidence and severity of AEs and laboratory abnormalities through ~~24 and 48~~ weeks • ~~Cumulative incidence of AEs by time to first occurrence~~ • Proportion of subjects who discontinue treatment due to AEs through ~~24 and 48~~ weeks
To evaluate the effects of DTG + 3TC once daily on fasting lipids over time compared to TBR	Change from Baseline in fasting lipids at Weeks 24 ~~and~~ 48
To assess viral resistance in subjects meeting Virologic Withdrawal Criteria	Incidence of observed genotypic and phenotypic resistance to ARVs for subjects meeting Virologic Withdrawal Criteria
To evaluate renal (in urine and blood) and bone (in blood) biomarkers in subjects treated with DTG + 3TC compared to TBR	Change from Baseline in renal and bone biomarkers at Weeks 24 ~~and~~ 48
To assess health related quality of life for subjects treated with DTG + 3TC compared to TBR	Change from Baseline in health status using EQ-5D-5L at Weeks 24 ~~and~~ 48 (or Withdrawal from the study)
Exploratory	
To evaluate the effect of patient characteristics (e.g., demographic factors, Baseline CD4) on antiviral and immunological responses to DTG + 3TC compared to TBR	• Proportion of subjects by subgroup(s) (e.g., by age, gender, Baseline CD4) with snapshot ~~virologic failure~~ at Weeks 24 ~~and~~ 48 • Change from Baseline in CD4+ cell counts at Weeks 24 ~~and~~ 48 by patient subgroups
To assess willingness to switch for subjects treated with DTG + 3TC compared to TBR	Reasons for Willingness to Switch at Day 1
To evaluate biomarkers of telomerase function in a subset of subjects treated with DTG + 3TC compared to TBR.	Change from baseline in biomarkers of telomerase function at Weeks 48 ~~and~~ 96
To evaluate inflammation biomarkers and insulin resistance in a subset of subjects treated with DTG+ 3TC compared to TBR	Change from Baseline in inflammation biomarkers and homeostasis model of assessment-insulin resistance (HOMA-IR) at Weeks 48 ~~and~~ 96

Objective	Endpoint
To evaluate the longer term antiviral and immunological effects, safety and tolerability of DTG + 3TC once daily in subjects treated with DTG + 3TC since the Early Switch Phase	For subjects in the DTG + 3TC arm since Early Switch Phase: • Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 96 using the Snapshot algorithm for the ITT-E population • Change from Baseline in CD4+ lymphocyte count and in CD4+/CD8+ cell count ratio at Week 96 • Incidence and severity of AEs and laboratory abnormalities over 96 weeks • Proportion of subjects who discontinue treatment due to AEs over 96 weeks • Incidence of disease progression (HIV associated conditions, AIDS and death) through Week 96 • Change from Baseline in renal and bone biomarkers at Week 96 • Change from baseline in biomarkers of inflammation, HOMA-IR and telomerase function at week 96
To evaluate the antiviral and immunological effects, safety and tolerability of DTG + 3TC for subjects switching in the Late Switch Phase	For subjects switching to DTG + 3TC in the Late Switch Phase: • Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 96 using the Snapshot algorithm for the ITT-E population • Change from Baseline in CD4+ lymphocyte count and in CD4+/CD8+ cell count ratio at Week 96 • Incidence and severity of AEs and laboratory abnormalities during the Late Switch Phase • Proportion of subjects who discontinue treatment due to AEs during the Late Switch Phase • Incidence of disease progression (HIV associated conditions, AIDS and death) during the Late Switch Phase • Change from Baseline in renal and bone biomarkers at Week 96 • Change from baseline in biomarkers of inflammation, HOMA-IR and telomerase function at week 96
To assess the steady-state DTG and 3TC exposure in HIV-1 infected patients	Steady state plasma PK parameters of DTG and 3TC will be assessed using intensive PK

Objective	Endpoint
	collected at week 4.
To characterize the DTG and 3TC steady-state PK of the DTG/3TC FDC in HIV-1 infected patients	Population estimates of DTG and 3TC PK parameters (e.g. apparent clearance [CL/F], apparent volume of distribution [V/F]) using DTG and 3TC intensive and sparse plasma concentrations at Weeks, 4, 8, 12, 24, 36 and 48

Current text:

Objective	Endpoint
Primary	
To demonstrate the non-inferior antiviral activity of switching to DTG +3TC once daily compared to continuation of TBR over 48 weeks in HIV-1 infected, ART therapy (ART)-experienced, virologically suppressed subjects	Virologic failure endpoint as per FDA snapshot category at Week 48
Secondary	
To demonstrate the antiviral activity of switching to DTG + 3TC once daily compared to continuation of TBR over 48 weeks	Proportion of subjects with plasma HIV-1 RNA <50 copies c/mL at Week 48 using the Snapshot algorithm for the ITT-E population
To demonstrate the antiviral activity of switching to DTG + 3TC once daily compared to continuation of TBR over 24**, 96 and 144** weeks	• Virologic failure endpoint as per FDA snapshot category at Week**s** 24**, 96 and 144** • Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week**s** 24**, 96 and 144** using the Snapshot algorithm for the ITT-E population
To evaluate the immune effects of DTG + 3TC once daily compared to continuation of TBR **over 24, 48, 96 and 144 weeks**	• Change from Baseline in CD4+ cell count and in CD4+/CD8+ cell count ratio at Weeks 24, 48**, 96 and 144** • Incidence of disease progression (HIV-associated conditions, AIDS, and death) through Weeks 24, 48**, 96 and 144**
To evaluate the safety and tolerability of DTG + 3TC once daily compared to TBR over time	• Incidence and severity of AEs and laboratory abnormalities through **144** weeks • Proportion of subjects who discontinue treatment due to AEs through **144** weeks
To evaluate the effects of DTG + 3TC once daily on fasting lipids over time compared to TBR	Change from Baseline in fasting lipids at Weeks 24, 48**, 96 and 144**
To assess viral resistance in subjects meeting Virologic Withdrawal Criteria	Incidence of observed genotypic and phenotypic resistance to ARVs for subjects meeting Virologic Withdrawal Criteria

Objective	Endpoint
To evaluate renal (in urine and blood) and bone (in blood) biomarkers in subjects treated with DTG + 3TC compared to TBR	Change from Baseline in renal and bone biomarkers at Weeks 24, 48**, 96 and 144**
To assess health related quality of life for subjects treated with DTG + 3TC compared to TBR	Change from Baseline in health status using EQ-5D-5L at Weeks 24, 48**, 96 and 144** (or Withdrawal from the study)

Objective	Endpoint
Exploratory	
To evaluate the effect of patient characteristics (e.g., demographic factors, Baseline CD4) on antiviral and immunological responses to DTG + 3TC compared to TBR	• Proportion of subjects by subgroup(s) (e.g., by age, gender, Baseline CD4) **with plasma HIV-1 RNA <50 c/mL using the** Snapshot **algorithm** at Weeks 24, 48**, 96 and 144** • Change from Baseline in CD4+ cell counts at Weeks 24, 48**, 96 and 144** by patient subgroups
To assess willingness to switch for subjects treated with DTG + 3TC compared to TBR	Reasons for Willingness to Switch at Day 1
To evaluate biomarkers of telomerase function in a subset of subjects treated with DTG + 3TC compared to TBR.	Change from baseline in biomarkers of telomerase function at Weeks 48**, 96 and 144**
To evaluate inflammation biomarkers and insulin resistance in a subset of subjects treated with DTG+ 3TC compared to TBR	Change from Baseline in inflammation biomarkers and homeostasis model of assessment-insulin resistance (HOMA-IR) at Weeks 48, 96 **and 144**
To evaluate the longer term antiviral and immunological effects, safety and tolerability of DTG + 3TC once daily in subjects treated with DTG + 3TC since the Early Switch Phase	For subjects in the DTG + 3TC arm since Early Switch Phase: • Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week **1**96 using the Snapshot algorithm for the ITT-E population • Change from Baseline in CD4+ lymphocyte count and in CD4+/CD8+ cell count ratio at Week **1**96 • Incidence and severity of AEs and laboratory abnormalities over **1**96 weeks • Proportion of subjects who discontinue treatment due to AEs over **1**96 weeks • Incidence of disease progression (HIV associated conditions, AIDS and death) through Week **1**96 • Change from Baseline in renal and bone biomarkers at Week **1**96 • Change from baseline in biomarkers of inflammation, HOMA-IR and telomerase function at week **1**96
To evaluate the antiviral and immunological effects, safety and tolerability of DTG + 3TC for subjects switching in the Late Switch Phase	For subjects switching to DTG + 3TC in the Late Switch Phase: • Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week **1**96 using the Snapshot algorithm for the ITT-E population • Change from Baseline in CD4+ lymphocyte count and in CD4+/CD8+ cell count ratio at Week **1**96

Objective	Endpoint
	• Incidence and severity of AEs and laboratory abnormalities during the Late Switch Phase • Proportion of subjects who discontinue treatment due to AEs during the Late Switch Phase • Incidence of disease progression (HIV associated conditions, AIDS and death) during the Late Switch Phase • Change from Baseline in renal and bone biomarkers at Week **1**96 • Change from baseline in biomarkers of inflammation, HOMA-IR and telomerase function at week **1**96
To assess the steady-state DTG and 3TC exposure in HIV-1 infected patients	Steady state plasma PK parameters of DTG and 3TC will be assessed using intensive PK collected at week 4.
To characterize the DTG and 3TC steady-state PK of the DTG/3TC FDC in HIV-1 infected patients	Population estimates of DTG and 3TC PK parameters (e.g. apparent clearance [CL/F], apparent volume of distribution [V/F]) using DTG and 3TC intensive and sparse plasma concentrations at Weeks, 4, 8, 12, 24, 36 and 48

Section 4.1 Study Design:

Previous text:

This is a ~~100~~-week, Phase III, randomized, open-label, active-controlled, multicenter, parallel-group study to assess the non-inferior antiviral activity and safety of replacing a TBR with a two-drug regimen of DTG + 3TC in HIV-infected adults who are virologically suppressed and stable on a TBR. The study will include a Screening Phase (up to 28 days), an Early Switch Phase (Day 1 up to Week ~~52~~), a Late Switch Phase (Week ~~52~~ up to Week ~~100~~), and a Continuation Phase (post Week ~~100~~). Approximately 550 HIV-1 infected adults who are on a stable TBR will be randomized 1:1 to switch to DTG + 3TC once daily (DTG + 3TC arm) for up to ~~100~~ weeks, or to continue their TBR for ~~52~~ weeks, at which time and if HIV-1 RNA <50 c/mL at Week ~~48~~ (or upon retest by Week ~~52~~), these subjects will switch to DTG + 3TC up to Week ~~100~~. For subjects randomized to the TBR, provisions will be in place, as needed and after discussion with the study team, to assist patients in obtaining their TBR during the study.

The primary endpoint for the study is the proportion of participants who meet the Snapshot virologic failure criteria at Week 48 using the Intent-to-Treat Exposed (ITT-E) population. The Week 48 primary analysis will take place after the last subject has had their Week 48 viral load assessed, including any retests. Subjects randomized to DTG + 3TC will receive DTG + 3TC up to Week ~~100~~. Subjects randomized to TBR will have a

Week ~~52~~ switch visit, allowing approximately 4 weeks for subjects who have a viral load ≥50 c/mL at Week ~~48~~ to have a retest prior to switch. The study will continue for at least ~~100~~ weeks.

~~All subjects who successfully complete up to 100 weeks of treatment will have the opportunity to continue receiving DTG + 3TC FDC once daily in a Continuation Phase as outlined in Section 4.2.4.~~

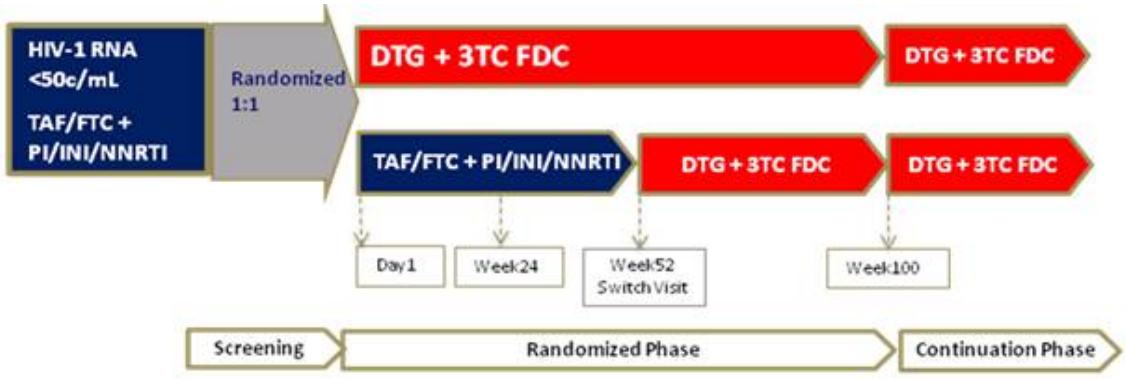
Current text:

This is a **200**-week, Phase III, randomized, open-label, active-controlled, multicenter, parallel-group study to assess the non-inferior antiviral activity and safety of replacing a TBR with a two-drug regimen of DTG + 3TC in HIV-infected adults who are virologically suppressed and stable on a TBR. The study will include a Screening Phase (up to 28 days), an Early Switch Phase (Day 1 up to Week **148**) a Late Switch Phase (**Week 148 up to Week 200**) and a Continuation Phase (post Week **2**00) **if DTG + 3TC FDC is not yet approved and available locally.** Approximately 550 HIV-1 infected adults who are on a stable TBR will be randomized 1:1 to switch to DTG + 3TC once daily (DTG + 3TC arm) for up to **200** weeks, or to continue their TBR for **148** weeks, at which time and if HIV-1 RNA <50 c/mL at Week **144** (or upon retest by Week **148**), these subjects will switch to DTG + 3TC up to Week **200**. For subjects randomized to the TBR, provisions will be in place, as needed and after discussion with the study team, to assist patients in obtaining their TBR during the study. **For subjects who switch to DTG + 3TC at Week 148, a separate Late Switch Phase Time and Events Table is provided in Section 7.1.2 as these participants will be monitored closely for the first 24 weeks post-switch. Subjects who remain on DTG + 3TC will follow a separate Late Switch Phase Time and Events Table in Section 7.1.3.**

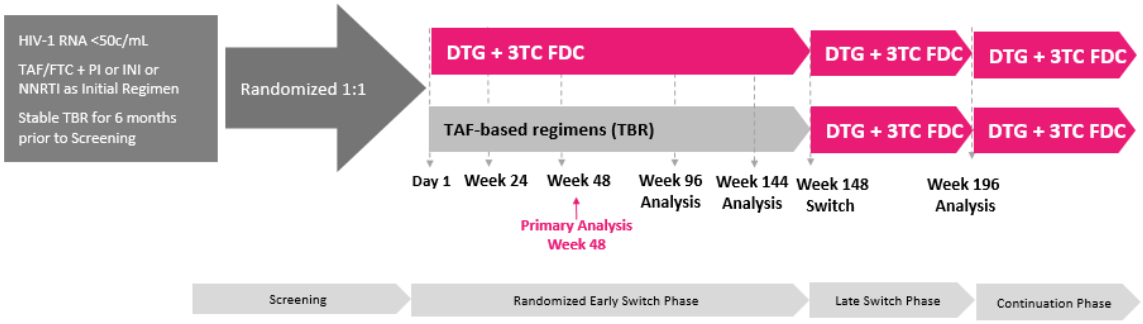
The primary endpoint for the study is the proportion of participants who meet the Snapshot virologic failure criteria at Week 48 using the Intent-to-Treat Exposed (ITT-E) population. The Week 48 primary analysis will take place after the last subject has had their Week 48 viral load assessed, including any retests. Subjects randomized to DTG + 3TC will receive DTG + 3TC up to Week **200**. Subjects randomized to TBR will have a Week **148** switch visit, allowing approximately 4 weeks for subjects who have a viral load ≥50 c/mL at Week **144** to have a retest prior to switch. The study will continue for at least **200** weeks.

All subjects who successfully complete 200 weeks of treatment will complete the study and transition to locally approved and available DTG + 3TC fixed-dose combination (FDC) and be managed as per standard of care at their study site. Prior to completion of the Week 200 visit, sites will need to have confirmation that DTG + 3TC FDC is locally available for study subjects. If DTG + 3TC FDC is not yet approved and available locally, ViiV Healthcare will continue to provide study drug in a Continuation Phase as outlined in Section 4.2.4.

Previous text:



Current text:



Section 4.2.2. Early Switch Phase

Previous text:

Early Switch Phase (Day 1 up to Week ~~52~~)

Subjects who fulfil all eligibility requirements will be randomly assigned 1:1 to receive DTG + 3TC FDC once daily up to Week ~~100~~, or continue their TBR up to Week ~~52~~. The DTG + 3TC and TBR will be administered in an open-label fashion throughout the study. For subjects randomized to the TBR, provisions will be in place, as needed and after discussion with the study team, to assist patients in obtaining their TBR during the study.

Following the Week ~~48~~ visit, subjects will stay on DTG + 3TC or their TBR for another 4 weeks so that the result from the Week ~~48~~ HIV-1 RNA testing is known. All subjects with a viral load ≥50 c/mL must have plasma HIV-1 RNA levels re-assessed within approximately 2-4 weeks. This will allow any subject in the TBR arm with a viral load ≥50 c/mL at Week ~~48~~ to have their viral load confirmed by a second measurement performed within approximately 2-4 weeks while still on their TBR regimen.

The primary analysis will take place after the last subject completes 52 weeks on therapy, to allow for the collection of a confirmatory viral load measurement in subjects presenting with HIV-1 RNA ≥50 c/mL at the Week 48 visit. If the retest HIV-1 RNA is <50 c/mL, then the subject will be considered to have met the criteria for virologic responder by Food Drugs and Administration (FDA)'s Snapshot algorithm at Week 48~~; such subjects in the TBR arm will be considered *eligible* to switch to DTG + 3TC at~~

~~Week 52~~. If the retest HIV-1 RNA is ≥50 c/mL, then the subject will be considered to be a virologic non-responder at Week 48 by Snapshot~~; such subjects in the TBR arm will be considered *ineligible* to switch to DTG + 3TC. Subjects who are ineligible to switch will be withdrawn from the study. Thus, the treatment extension up to Week 52 will allow for as complete an assessment as possible of treatment response in the primary endpoint analysis at Week 48 within the Snapshot window.~~

The secondary analyses at Week 24 will take place after the last subject completes 28 weeks on therapy, as needed, to allow for the collection of a confirmatory viral load measurement in subjects presenting with HIV-1 RNA ≥50 c/mL at Week 24.

Current text:

Early Switch Phase (Day 1 up to Week **148**)

Subjects who fulfil all eligibility requirements will be randomly assigned 1:1 to receive DTG + 3TC FDC once daily up to Week **200**, or continue their TBR up to Week **148**. The DTG + 3TC and TBR will be administered in an open-label fashion throughout the study. For subjects randomized to the TBR, provisions will be in place, as needed and after discussion with the study team, to assist patients in obtaining their TBR during the study.

Following the Week **144** visit, subjects will stay on DTG + 3TC or their TBR for another 4 weeks so that the result from the Week 1**44** HIV-1 RNA testing is known. All subjects with a viral load ≥50 c/mL must have plasma HIV-1 RNA levels re-assessed within approximately 2-4 weeks. This will allow any subject in the TBR arm with a viral load ≥50 c/mL at Week **144** to have their viral load confirmed by a second measurement performed within approximately 2-4 weeks while still on their TBR regimen.

The primary analysis will take place after the last subject completes **up to** 52 weeks on therapy, to allow for the collection of a confirmatory viral load measurement in subjects presenting with HIV-1 RNA ≥50 c/mL at the Week 48 visit. If the retest HIV-1 RNA is <50 c/mL, then the subject will be considered to have met the criteria for virologic responder by Food Drugs and Administration (FDA)'s Snapshot algorithm at Week 48. If the retest HIV-1 RNA is ≥50 c/mL, then the subject will be considered to be a virologic non-responder at Week 48 by Snapshot.

The secondary analys**i**s at Week 24 will take place after the last subject completes **up to** 28 weeks on therapy, as needed, to allow for the collection of a confirmatory viral load measurement in subjects presenting with HIV-1 RNA ≥50 c/mL at Week 24.

The secondary analysis at Week 96 will take place after the last subject completes up to 100 weeks on therapy, as needed, to allow for the collection of a confirmatory viral load measurement in subjects presenting with HIV-1 RNA ≥50 c/mL at Week 96.

The secondary analysis at Week 144 will take place after the last subject completes up to 148 weeks on therapy, as needed, to allow for the collection of a confirmatory

viral load measurement prior to Week 148 switch visit in subjects presenting with HIV-1 RNA ≥50 c/mL at Week 144. If the retest HIV-1 RNA is <50 c/mL, subjects in the TBR arm will be considered eligible to switch to DTG + 3TC at Week 148. If the retest HIV-1 RNA is ≥50 c/mL, the subjects in the TBR arm will be considered ineligible to switch to DTG + 3TC. Subjects who are ineligible to switch will be withdrawn from the study. Thus, the treatment extension up to Week 148 will allow for as complete an assessment as possible of treatment response in the analysis at Week 144 within the Snapshot window.

Section 4.2.3 Late Switch Phase

Previous text:

Late Switch Phase (Week ~~52~~ to Week ~~100~~)

At Week ~~48~~, subjects randomly assigned to DTG + 3TC and with HIV-1 RNA <50 c/mL will continue on that treatment through Week ~~100~~. At Week ~~52~~, subjects randomly assigned to continue their TBR and with HIV-1 RNA <50 c/mL at Week ~~48~~ will switch to DTG + 3TC once daily and be followed up to Week ~~100~~.

The analyse~~s~~ at Week 96 will take place after the last subject completes ~~100~~ weeks on therapy, as needed, to allow for the collection of a confirmatory viral load measurement in subjects presenting with HIV-1 RNA ≥50 c/mL at Week 96.

Current text:

Late Switch Phase (Week **148** to Week **200**)

At Week **144**, subjects randomly assigned to DTG + 3TC and with HIV-1 RNA <50 c/mL will continue on that treatment through Week **200**. At Week **148**, subjects randomly assigned to continue their TBR and with HIV-1 RNA <50 c/mL at Week **144 (or upon retest)** will switch to DTG + 3TC once daily and be followed up to Week **200**. **For subjects who switch to DTG + 3TC at Week 148, a separate Late Switch Phase Time and Events Table is provided in Section 7.1.2 as these participants will be monitored closely for the first 24 weeks post-switch. Subjects who remain on DTG + 3TC will follow a separate Late Switch Phase Time and Events Table in Section 7.1.3.**

The analys**i**s at Week **1**96 will take place after the last subject completes **200** weeks on therapy, as needed, to allow for the collection of a confirmatory viral load measurement in subjects presenting with HIV-1 RNA ≥50 c/mL at Week **1**96.

Section 4.2.4 Continuation Phase (Post Week 200)

Previous text:

~~All subjects who successfully complete 100 weeks of treatment will have the opportunity to receive DTG + 3TC FDC once daily in a Continuation Phase until:~~

- DTG ~~and~~ 3TC ~~are each~~ locally approved for use as ~~part of a dual~~ regimen, and ~~each of the single entities of DTG and 3TC are~~ available to subjects (e.g., through public health services or through their usual health insurance payer), or
- ~~the actual 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.

~~The purpose of the Continuation Phase is to ensure provision of DTG and 3TC.~~
Assessments during the Continuation Phase are limited and will include plasma HIV-1 RNA and collection of AEs/SAEs.

Current text:

At the end of the study at Week 200, subjects will transition to locally approved and available DTG + 3TC FDC and be managed as per standard of care at their study site. Prior to completion of the Week 200 visit, sites will need to have confirmation that DTG + 3TC FDC is locally available for study subjects. If DTG + 3TC FDC is not yet approved and available locally, ViiV Healthcare will continue to provide study drug in a Continuation Phase until:

- DTG + 3TC **FDC is** locally approved for use as **a 2-drug** regimen, and available to subjects (e.g., through public health services or through their usual health insurance payer), 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.

Assessments during the Continuation Phase are limited and will include plasma HIV-1 RNA and collection of AEs/SAEs.

Section 4.3 Type and Number of Subjects

Previous text: The study closed screening on 18 May 2018 with a total of 933 screened subjects and ~~based on current randomisation numbers and current screen failure rate a total of approximately 750 subjects are expected to be randomised.~~

Current text: The study closed screening on 18 May 2018 with a total of 933 screened subjects and **a total of 743 subjects were randomized.**

Section 4.4 Design Justification:

Previous text:
In this study, subjects will be randomized 1:1 to switch to DTG + 3TC from a TBR at Day 1 or stay on their TBR for up to ~~52~~ weeks. The primary endpoint will be evaluated at Week 48 using a 4% non-inferiority (NI) margin. This study is evaluating the rate of

Snapshot algorithm measured virological failure in already suppressed subjects to test the hypothesis that maintenance of the suppression of HIV-1 replication by DTG + 3TC will be non-inferior to that observed in the TBR arm of the study through Week 48. To assess the durability of HIV-1 RNA suppression by DTG + 3TC, subjects will remain on DTG + 3TC through Week ~~100~~.

Current text:
In this study, subjects will be randomized 1:1 to switch to DTG + 3TC from a TBR at Day 1 or stay on their TBR for up to **148** weeks. The primary endpoint will be evaluated at Week 48 using a 4% non-inferiority (NI) margin. This study is evaluating the rate of Snapshot algorithm measured virological failure in already suppressed subjects to test the hypothesis that maintenance of the suppression of HIV-1 replication by DTG + 3TC will be non-inferior to that observed in the TBR arm of the study through Week 48. To assess the durability of HIV-1 RNA suppression by DTG + 3TC, subjects will remain on DTG + 3TC through Week **200**.

After Week 96, study visits will be extended to every 6 months (instead of 12 weekly visits) except in countries where visits are required every 3 months per standard of care. For subjects who switch to DTG + 3TC at Week 148, a separate Late Switch Phase Time and Events Table is provided in Section 7.1.2 as these participants will be monitored closely for the first 24 weeks post-switch. Subjects who remain on DTG + 3TC will follow a separate Late Switch Phase Time and Events Table in Section 7.1.3.

This amended design will allow a longer period of comparison of antiviral efficacy, safety and tolerability between DTG + 3TC and TAF-based regimens. Long-term comparison of outcomes between regimens is important in a disease where treatment is provided life-long.

Section 4.6.1 Risk Assessment:

Previous text:

DTG: Neural tube defects	In one ongoing birth outcome surveillance study in Botswana, early results from an unplanned interim analysis show that 4/426 (0.9%) of women who were taking DTG when they became pregnant had babies with neural tube defects compared to a background rate of 0.1%.	1. A female subject is eligible to participate if she is not pregnant, not lactating, and, if she is a female of reproductive potential, agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see Appendix 3, Section 13.3.1) from 30 days prior to the first dose of study medication and for at least 2 weeks after the last dose of study medication. 2. Women who are breastfeeding or plan to become pregnant or breastfeed

		during the study are excluded. 3. Women who become pregnant, or who desire to be pregnant while in the study, or who state they no longer are willing to comply with the approved pregnancy avoidance methods, will have study treatment discontinued and will be withdrawn from the study. 4. Females of reproductive potential are reminded re: pregnancy avoidance and adherence to contraception requirements at every study visit. 5. Pregnancy status is monitored at every study visit

Current text:

DTG: Neural tube defects	In one ongoing birth outcome surveillance study in Botswana, early results from an unplanned interim analysis show that 4/426 (0.9%) of women who were taking DTG when they became pregnant had babies with neural tube defects compared to a background rate of 0.1%.	1. A female subject is eligible to participate if she is not pregnant, not lactating, and, if she is a female of reproductive potential, agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see Appendix 3, Section 13.3.1) from 30 days prior to the first dose of study medication and for at least 2 weeks after the last dose of study medication. 2. Women who are breastfeeding or plan to become pregnant or breastfeed during the study are excluded. 3. Women who become pregnant, or who desire to be pregnant while in the study, or who state they no longer are willing to comply with the approved pregnancy avoidance methods, will have study treatment discontinued and will be withdrawn from the study. 4. Females of reproductive potential are reminded re: pregnancy avoidance and adherence to contraception requirements at every study visit. 5. Pregnancy status is monitored at every study visit **and using home-based urine pregnancy tests at approximately 12 week intervals when study visits are extended to every 24 weeks.**

Section 5.4 Withdrawal and Stopping Criteria:

Previous text:

- For subjects in the TBR arm during the Early Switch Phase, plasma HIV-1 RNA ≥50 c/mL at Week ~~48~~ with a confirmatory retest (see Section 5.4)

Current text:

- For subjects in the TBR arm during the Early Switch Phase, plasma HIV-1 RNA ≥50 c/mL at Week **144** with a confirmatory retest (see Section 5.4)

Section 5.5 Subject and Study Completion:

Previous text:

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

- Randomly assigned to either treatment group, completed the ~~Randomized~~ Phase at the Week ~~100~~ visit, and did not enter the Continuation Phase;

- Randomly assigned to either treatment group, completed the Randomized Phase at the Week ~~1~~00 visit, entered and completed the Continuation Phase, defined as remaining on study until:

    - DTG ~~and~~ 3TC ~~are~~ each locally approved for use as ~~part of a dual~~ regimen, and ~~each of the single entities of DTG and 3TC are~~ available through public health services or through the subject's usual health insurance payer, or
    - ~~the actual 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.

Current text:

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

- Randomly assigned to either treatment **group** and completed the **Late Switch** Phase at the Week **200** visit, and did not enter the Continuation Phase;

- Randomly assigned to either treatment group, completed the Randomized Phase at the Week **2**00 visit, entered and completed the Continuation Phase, defined as remaining on study until:

    - DTG + 3TC **FDC tablet is** locally approved for use as **a 2-drug** regimen, and available through public health services or through the subject's usual health insurance payer, 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.

Section 6.1 Study treatment: Investigational Product and Other Study Treatment:

Previous text:

The investigational study drugs DTG and 3TC will be supplied by GSK/ViiV Healthcare as the fixed dose combination tablet DTG + 3TC. Subjects randomly assigned to continue their TBR for up to ~~52~~ weeks will not have drug provided as clinical trial material.

Current text:

The investigational study drugs DTG and 3TC will be supplied by GSK/ViiV Healthcare as the fixed dose combination tablet DTG + 3TC. Subjects randomly assigned to continue their TBR for up to **148** weeks will not have drug provided as clinical trial material.

Previous text:

	Study Treatment (Open Label Randomised Phase, Day 1 to Week ~~100~~)

Current text:

	Study Treatment (Open Label Randomised Phase, Day 1 to Week **200**)

Section 6.10 Treatment after the end of the Study:

Previous text:

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 is providing specific post-study treatment.~~

~~All subjects who successfully complete 100 weeks of treatment will continue to have access to DTG + 3TC FDC in the Continuation Phase until:~~

- ~~DTG and 3TC are each locally approved for use as part of a dual regimen, and each of the single entities of DTG and 3TC are available to subjects (e.g., through public health services or through their usual health insurance payer), or~~
- ~~the actual 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.~~

~~The purpose of the Continuation Phase is to ensure provision of DTG + 3TC.~~ Assessments during the Continuation Phase are limited (see Time and Events schedule, Section 7.1).

Current text:

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition. **At the end of the study at Week 200, subjects will transition to locally approved and available DTG + 3TC FDC and be managed as per standard of care at their study site. Prior to completion of the Week 200 visit, sites will need to have confirmation that DTG + 3TC FDC is locally available for study subjects. If DTG + 3TC FDC is not yet approved and available locally, ViiV Healthcare will continue to provide study drug in a Continuation Phase until local availability.**

Assessments during the Continuation Phase are limited (see Time and Events schedule, Section 7.1).

Section 6.11.2 Prohibited Medications and Non-Drug Therapies:

Previous text:

- Systemically administered immunomodulators (such as interleukin and interferon agents) are prohibited through Week ~~96~~ (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.

Current text:

- Systemically administered immunomodulators (such as interleukin and interferon agents) are prohibited through Week **200** (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.

Section 7.1 Time and Events Table:

Added level 3 headings: Early Switch Phase Time and Events Table (Screening to Week 148); Late Switch Phase Time and Events Table: TBR subjects who switched to DTG + 3TC at Week 148; Late Switch Phase Time and Events Table: DTG + 3TC arm

Added text: TBR subjects switching at Week 148 are followed up at 4, 12 and 24 weeks post-switch after which 24 weekly visits are resumed.

Previous text: Please note updates to sequence of footnotes are not marked in the table in strikethrough text.

Procedures	**Screening Visit**[a]	**Open-label Randomised Phase**													**~~Continuation Phase~~**[c]	**Withdrawal**	**Follow-up**[d]
		Baseline / Day 1	**Week**														
			4	**8**	**12**	**24**	**36**	**48**	**~~52 Switch Visit~~**[b]	**60**	**72**	**84**	**96**	**100**	**~~Every 12 weeks after Week 100~~**		
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																
Body Weight (BMI will be calculated within the eCRF)	X	X	X	X	X	X	X	X	~~X~~	X	X	X	X	X	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	
Columbia Suicidality Severity Rating Scale		X[h]	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
Symptom Directed Physical Exam[i]	X	X	X	X	X	X	X	X		X	X	X	X	X		X	X
12-lead ECG[j]	X																
Adverse events		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
Willingness to Switch[l]		X[l]															
EQ-5D-5L[m]		X	X			X		X					X			X	

Procedures	Screening Visit[a]	Open-label Randomised Phase													~~Continuation Phase~~[c]	Withdrawal	Follow-up[d]
		Baseline / Day 1	Week														
			4	8	12	24	36	48	~~52 Switch Visit~~[b]	60	72	84	96	100	~~Every 12 weeks after Week 100~~		
Laboratory Assessments																	
Quantitative plasma HIV-1 RNA[n]	X	X	X	X	X	X	X	X		X	X	X	X		X	X	
Lymphocyte subset (CD4+ at all visits and CD8+ at Baseline, and Weeks 24, 48 and 96 only)	X	X	X	X	X	X	X	X		X	X	X	X			X	
Plasma for storage[o]	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
Hematology	X	X	X	X	X	X	X	X		X	X	X	X	X		X	X
PT/INR	X																
Fasting lipids and glucose[p]		X				X		X					X			X[q]	
Urinalysis and spot urine for protein analysis[r]		X				X		X					X			X	X
Pregnancy test[s,t]	S	U/S[u]	S	S	S	S	S	S	~~U~~	S	S	S	S	S	S	S	
HbsAg, anti-HBc, anti-HBs, and HBV DNA[v]	X																
HCV antibody	X																
RPR	X																
Insulin, HbA1c and renal, and bone marker analytes (blood/urine)[w]		X				X		X					X			X[q]	
Whole Blood (Virology)[x]		X						X					X			X	
Whole Blood (Telomere length)[y]		X						X					X			X[z]	
Cryopreserved PBMCs[aa]		X						X					X			X[z]	
Inflammation biomarkers (Blood) [bb]		X						X					X			X[w]	
Study Treatment																	
IVRS/IWRS[cc]	X	X	X	X	X	X	X	X	~~X~~	X	X	X	X	X	X	X	X

Procedures	**Screening Visit**[a]	**Open-label Randomised Phase**													**~~Continuation Phase~~**[c]	**Withdrawal**	**Follow-up**[d]
		Baseline / Day 1	**Week**														
			4	**8**	**12**	**24**	**36**	**48**	**~~52~~ ~~Switch Visit~~**[b]	**60**	**72**	**84**	**96**	**100**	**~~Every 12 weeks after Week 100~~**		
Dispense study treatment		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	
Pharmacokinetic[dd]																	
Intensive PK sample collection at selected sites for subset of ~30 subjects (Fasting)[dd]			X[ee]														
Dispense PK Diary Card to intensive PK sub-set		X															
Sparse PK sample collection[dd]			X[ff]	X	X	X	X	X									
Dispense PK Diary Card to Sparse PK subjects		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, HbA1c = Glycated hemoglobin, HBsAg = hepatitis B surface antigen, HCV = hepatitis C virus, HIV-1 = human immunodeficiency virus type 1, IVRS = interactive voice recognition system, IWRS = interactive web recognition system, PBMC = peripheral blood mononuclear cell, RNA = ribonucleic acid, RPR = rapid plasma reagin

a. As soon as all Screening results are available, randomization may occur.

b. Subjects with plasma HIV-1 RNA ≥50 c/mL at Week ~~48~~ (primary endpoint) must have HIV-1 RNA level re-assessed by a second measurement performed 2-4 weeks later. Subjects should have received full doses of study treatment for at least 2 weeks at the time of HIV-1 RNA re-assessment. Subjects randomized to DTG + 3TC do not attend a Week ~~52~~ switch visit.

~~c. All subjects who complete through Week 100 will have the opportunity to 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. Genotypic resistance testing results MUST be provided to ViiV after screening and before randomization.

f. Full medical history will be conducted prior to randomization 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. BMI will be calculated within the eCRF.
h. On Day 1, the electronic Columbia Suicidality Severity Rating Scale eC-SSRS, patient completed questionnaire) is to be administered prior to randomization.
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/GSK product will be collected between obtaining informed consent and administration of study drug at Day 1.
l. Willingness to Switch Survey must be done prior to randomization.
m. Questionnaire/Surveys are recommended to be administered at the beginning of the visit before any other assessments are conducted. Only conduct questionnaires/surveys at Withdrawal if occurring prior to Week 96.
n. See Virologic Withdrawal and Stopping Criteria Section of protocol (Section 5.4).
o. Plasma samples for storage will be collected at each visit starting at Screening, including unscheduled visits (e.g. for HIV-1 RNA levels and immunological parameters). These samples will be used when needed such as when samples are lost, arrive at the laboratory unevaluable, or for genotypic and/or phenotypic analyses when subjects meet Suspected and Confirmed Virologic Withdrawal criteria.
p. An overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable.
q. Collect sample for these assessments ONLY if the Withdrawal visit occurs at Week 24, 48 ~~or~~ 96.
r. A morning specimen is preferred. To assess renal biomarkers: urine albumin/creatinine ratio; urine protein/creatinine ratio; and urine phosphate.
s. Women of childbearing potential only. S=serum, U=urine. Pregnancy events will be captured starting at Day 1 following exposure to study drug.
t. Remind females of reproductive potential of the need to avoid pregnancy while in study and adherence to the study's contraception requirements.
u. Local serum pregnancy test on Day 1 is allowed if it can be done, and results obtained, within 24 hours prior to randomization
v. 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.
w. Blood sample for insulin, HbA1c, and renal and bone biomarker assessments: **Renal:** Cystatin C; Beta-2-Microglobulin; Retinol Binding Protein (RBP); **Bone:** bone specific alkaline phosphatase, procollagen type 1-N-propeptide, type 1 collagen cross-linked C-telopeptide, osteocalcin, 25 hydroxy-Vitamin D.
x. Whole blood (Virology) may be used for virologic analyses as described in the protocol.
y. Whole blood will be used for telomere length evaluation at Day 1, Week 48, Week 96, and at the Withdrawal visit.
z. Collect sample for these assessments ONLY if the Withdrawal visit occurs at Week 48 ~~or~~ 96
aa. PBMCs will be collected, cryopreserved and stored in a subset of sites. These samples will be used for the measurement of telomerase activity.
bb. Blood sample for inflammation biomarker assessments: IL-6, hs-CRP, d dimer, sCD14, sCD163.
cc. At Screening, a subject number will be generated.
dd. PK sampling in subjects from the DTG/3TC FDC arm only, as detailed in Section 11.
ee. Intensive PK sampling in a subset of subjects from the DTG/3TC FDC arm at select sites at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 10 and 24 hours post-dose. On the intensive PK day, patients are required to fast from 8 hours prior to dosing and then through 4 hours post-dose. Detailed in Section 11.
ff. At Week 4, subjects who performed intensive PK do not perform Sparse PK sampling.

Current text: Please note updates to sequence of footnotes are not marked in the table in bold text.

Procedures	Screening Visit[a]	Open-label Randomised **Early Switch** Phase														**Switch Visit**	Withdrawal	Follow-up[d]
		Baseline / Day 1	Week															
			4	8	12	24	36	48	60	72	84	96	**108 (optional)[b]**	**120**	**132 (optional)[b]**	**144**	**148[c]**	
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																	
Body Weight (BMI will be calculated within the eCRF)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	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	
Columbia Suicidality Severity Rating Scale		X[h]	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

Procedures	Screening Visit[a]	Open-label Randomised **Early Switch** Phase															**Switch Visit**	Withdrawal	Follow-up[d]
		Baseline / Day 1	Week																
			4	8	12	24	36	48	60	72	84	96	**108 (optional)[b]**	**120**	**132 (optional)[b]**	**144**	**148[c]**		
Symptom Directed Physical Exam[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
12-lead ECG[j]	X																		
Adverse events		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
Willingness to Switch[l]		X[l]																	
EQ-5D-5[m]		X	X			X		X				X				X		X	
Laboratory Assessments																			
Quantitative plasma HIV-1 RNA[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Lymphocyte subset (CD4+ at all visits and CD8+ at Baseline, and Weeks 24, 48, 96, 144 and 196 only)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Plasma for storage[o]	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
Hematology	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[p]		X				X		X				X				X		X[q]	
Urinalysis and spot urine for protein analysis[r]		X				X		X				X				X		X	X
Pregnancy test[s,t,u]	S	U/S[v]	S	S	S	S	S	S	S	S	S	S	S	S	S	S	U	S	
HbsAg, anti-HBc, anti-HBs, and HBV DNA[w]	X																		

Procedures	Screening Visit[a]	Open-label Randomised **Early Switch** Phase															**Switch Visit**	Withdrawal	Follow-up[d]
		Baseline / Day 1	Week																
			4	8	12	24	36	48	60	72	84	96	**108 (optional)[b]**	**120**	**132 (optional)[b]**	**144**	**148[c]**		
HCV antibody	X																		
RPR	X																		
Insulin, HbA1c and renal, and bone marker analytes (blood/urine)[x]		X				X		X				X				X		X[q]	
Whole Blood (Virology)[y]		X						X				X				X		X	
Whole Blood (Telomere length)[z]		X						X				X				X		X[aa]	
Cryopreserved PBMCs[bb]		X						X				X				X		X[aa]	
Inflammation biomarkers (Blood)[cc]		X						X				X				X		X[aa]	
Study Treatment																			
IVRS/IWRS[dd]	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		
Study treatment accountability (pill counts)			X	X	X	X	X	X	X	X	X	X		X		X		X	
Pharmacokinetic[ee]																			
Intensive PK sample collection at selected sites for subset of ~30 subjects (Fasting)[ee]			X[ff]																
Dispense PK Diary Card to intensive PK sub-set		X																	

Procedures	Screening Visit[a]	Open-label Randomised **Early Switch** Phase														**Switch Visit**	Withdrawal	Follow-up[d]
		Baseline / Day 1	Week 4	8	12	24	36	48	60	72	84	96	**108 (optional)[b]**	**120**	**132 (optional)[b]**	**144**	**148[c]**		
Sparse PK sample collection[ee]			X[gg]	X	X	X	X	X											
Dispense PK Diary Card to Sparse PK subjects		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, HbA1c = Glycated hemoglobin, HBsAg = hepatitis B surface antigen, HCV = hepatitis C virus, HIV-1 = human immunodeficiency virus type 1, IVRS = interactive voice recognition system, IWRS = interactive web recognition system, PBMC = peripheral blood mononuclear cell, RNA = ribonucleic acid, RPR = rapid plasma reagin																		

Procedures	**Late Switch Phase through End of Study**						**Continuation Phase**	**Withdrawal**	**Follow-up**
	Week								
	152	**160**	**172**	**184 (optional)[b]**	**196**	**200[hh]**	**Every 24 weeks after Week 200[b,ii]**		
Clinical and Other Assessments									
Body Weight (BMI will be calculated within the eCRF)	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
HIV associated conditions	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Columbia Suicidality Severity Rating Scale	**X**	**X**	**X**	**X**	**X**		**X**	**X**	
Concomitant medication	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Symptom Directed Physical Exam[i]	**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**
Adverse events	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Serious adverse events	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
EQ-5D-5L[m]					**X**			**X**	
Laboratory Assessments									

Procedures	Late Switch Phase through End of Study						Continuation Phase	Withdrawal	Follow-up
	Week								
	152	160	172	184 (optional)[b]	196	200[hh]	Every 24 weeks after Week 200[b,ii]		
Quantitative plasma HIV-1 RNA[n]	X	X	X	X	X		X	X	
Lymphocyte subset (CD4+ at all visits and CD8+ at Baseline, and Weeks 24, 48, 96, 144 and 196 only)	X	X	X	X	X			X	
Plasma for storage[o]	X	X	X	X	X		X	X	
Clinical chemistry	X	X	X	X	X	X		X	X
Hematology	X	X	X	X	X	X		X	X
Fasting lipids and glucose[p]					X			X[q]	
Urinalysis and spot urine for protein analysis[r]					X			X	X
Pregnancy test[s,t,u]	S	S	S	S	S	S	S	S	
Insulin, HbA1c and renal, and bone marker analytes (blood/urine)[x]					X			X[q]	
Whole Blood (Virology)[y]					X			X	
Whole Blood (Telomere length)[z]					X			X[aa]	
Cryopreserved PBMCs[bb]					X			X[aa]	
Inflammation biomarkers (Blood)[cc]					X			X[aa]	
Study Treatment									
IVRS/IWRS[dd]	X	X	X	X	X	X	X	X	X
Dispense study treatment	X	X	X		X		X		
Study treatment accountability (pill counts)	X	X	X		X	X	X	X	

Procedures	Late Switch Phase through End of Study					Continuation Phase	Withdrawal	Follow-up
	Week							
	160 (optional)[b]	172	184 (optional)[b]	196	200[hh]	Every 24 weeks after Week 200[b,ii]		
Clinical and Other Assessments								
Body Weight (BMI will be calculated within the eCRF)	X	X	X	X	X	X	X	X
HIV associated conditions	X	X	X	X	X	X	X	
Columbia Suicidality Severity Rating Scale	X	X	X	X		X	X	
Concomitant medication	X	X	X	X	X	X	X	X
Symptom Directed Physical Exam[i]	X	X	X	X	X		X	X
Adverse events	X	X	X	X	X	X	X	X
Serious adverse events	X	X	X	X	X	X	X	X
EQ-5D-5L[m]				X			X	
Laboratory Assessments								
Quantitative plasma HIV-1 RNA[n]	X	X	X	X		X	X	
Lymphocyte subset (CD4+ at all visits and CD8+ at Baseline, and Weeks 24, 48, 96, 144 and 196 only)	X	X	X	X			X	
Plasma for storage[o]	X	X	X	X		X	X	
Clinical chemistry	X	X	X	X	X		X	X
Hematology	X	X	X	X	X		X	X
Fasting lipids and glucose[p]				X			X[q]	
Urinalysis and spot urine for protein analysis[r]				X			X	X
Pregnancy test[s,t,u]	S	S	S	S	S	S	S	
Insulin, HbA1c and renal, and bone marker analytes (blood/urine)[x]				X			X[q]	
Whole Blood (Virology)[y]				X			X	
Whole Blood (Telomere length)[z]				X			X[aa]	
Cryopreserved PBMCs[bb]				X			X[aa]	
Inflammation biomarkers (Blood)[cc]				X			X[aa]	
Study Treatment								
IVRS/IWRS[dd]	X	X	X	X	X	X	X	X

Procedures	Late Switch Phase through End of Study					Continuation Phase	Withdrawal	Follow-up
	Week							
	160 (optional)[b]	172	184 (optional)[b]	196	200[hh]	Every 24 weeks after Week 200[b,ii]		
Dispense study treatment		X		X		X		
Study treatment accountability (pill counts)		X		X	X	X	X	

a. As soon as all Screening results are available, randomization may occur.

b. This optional study visit is ONLY to be conducted in countries that require visits every 3 months per standard of care.

c. Subjects with plasma HIV-1 RNA ≥50 c/mL at Week **144** must have HIV-1 RNA level re-assessed by a second measurement performed 2-4 weeks later. Subjects should have received full doses of study treatment for at least 2 weeks at the time of HIV-1 RNA re-assessment. Subjects randomized to DTG + 3TC do not attend a Week **148** switch visit.

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. **Only the laboratory tests necessary to evaluate the AE/SAE/laboratory abnormality should be collected.**

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. Genotypic resistance testing results MUST be provided to ViiV after screening and before randomization.

f. Full medical history will be conducted prior to randomization 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. BMI will be calculated within the eCRF.

h. On Day 1, the electronic Columbia Suicidality Severity Rating Scale eC-SSRS, patient completed questionnaire) is to be administered prior to randomization.

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/GSK product will be collected between obtaining informed consent and administration of study drug at Day 1.

l. Willingness to Switch Survey must be done prior to randomization.

m. Questionnaire/Surveys are recommended to be administered at the beginning of the visit before any other assessments are conducted. Only conduct questionnaires/surveys at Withdrawal if occurring prior to Week **196**.

n. See Virologic Withdrawal and Stopping Criteria Section of protocol (Section 5.4).

o. Plasma samples for storage will be collected at each visit starting at Screening, including unscheduled visits (e.g. for HIV-1 RNA levels and immunological parameters). These samples will be used when needed such as when samples are lost, arrive at the laboratory unevaluable, or for genotypic and/or phenotypic analyses when subjects meet Suspected and Confirmed Virologic Withdrawal criteria.

p. An overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable.
q. Collect sample for these assessments ONLY if the Withdrawal visit occurs at Week 24, 48, 96**, 144 or 196**.
r. A morning specimen is preferred. To assess renal biomarkers: urine albumin/creatinine ratio; urine protein/creatinine ratio; and urine phosphate.
s. Women of childbearing potential only. S=serum, U=urine. Pregnancy events will be captured starting at Day 1 following exposure to study drug.
t. Remind females of reproductive potential of the need to avoid pregnancy while in study and adherence to the study's contraception requirements.
u. Beginning after Week 96, if study visits are every 24 weeks, participants who are women of child bearing potential must also do a home-based urine pregnancy test approximately every 12 weeks between study visits at approximately Weeks 108, 132, 160 and 184 and during the Continuation Phase. Site staff must contact the participants who are women of child bearing potential to remind them to complete the test and to verify and record pregnancy test results in the source documents. The site must also complete the pregnancy status eCRF if a pregnancy occurs and report the pregnancy to ViiV/GSK per Section 13.3.2.
v. Local serum pregnancy test on Day 1 is allowed if it can be done, and results obtained, within 24 hours prior to randomization
w. 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.
x. Blood sample for insulin, HbA1c, and renal and bone biomarker assessments: **Renal:** Cystatin C; Beta-2-Microglobulin; Retinol Binding Protein (RBP); **Bone:** bone specific alkaline phosphatase, procollagen type 1-N-propeptide, type 1 collagen cross-linked C-telopeptide, osteocalcin, 25 hydroxy-Vitamin D.
y. Whole blood (Virology) may be used for virologic analyses as described in the protocol.
z. Whole blood will be used for telomere length evaluation at Day 1, Week 48, Week 96, **Week 144, Week 196** and at the Withdrawal visit.
aa. Collect sample for these assessments ONLY if the Withdrawal visit occurs at Week 48, 96, **144 or 196**
bb. PBMCs will be collected, cryopreserved and stored in a subset of sites. These samples will be used for the measurement of telomerase activity.
cc. Blood sample for inflammation biomarker assessments: IL-6, hs-CRP, d dimer, sCD14, sCD163.
dd. At Screening, a subject number will be generated.
ee. PK sampling in subjects from the DTG/3TC FDC arm only, as detailed in Section 11.
ff. Intensive PK sampling in a subset of subjects from the DTG/3TC FDC arm at select sites at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 10 and 24 hours post-dose. On the intensive PK day, patients are required to fast from 8 hours prior to dosing and then through 4 hours post-dose. Detailed in Section 11.
gg. At Week 4, subjects who performed intensive PK do not perform Sparse PK sampling.
hh. Subjects must return to the clinic for a Week 200 End of Study visit when transitioning to commercial supplies or to an alternate ART regimen, if appropriate. Do not dispense study treatment at this study completion visit unless the participant is entering the Continuation Phase.
ii. Only in case of non-availability of DTG + 3TC FDC. 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.

Section 7.3.1.2 Secondary Efficacy Endpoints:

Previous text:

- Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Weeks 24 ~~and~~ 48 using the Snapshot algorithm for the ITT-E population
- Percentage of subjects with viral failure endpoint as per FDA snapshot category at Weeks 24
- Change from Baseline in CD4+ lymphocyte count at Weeks 24 ~~and~~ 48
- Change from Baseline in CD8+ lymphocyte count and CD4+/CD8+ cell counts ratio at Weeks 24 ~~and~~ 48
- Incidence of disease progression (HIV-associated conditions, AIDS and death).

Current text:

- Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Weeks 24,48**, 96 and 144** using the Snapshot algorithm for the ITT-E population
- Percentage of subjects with viral failure endpoint as per FDA snapshot category at Week**s** 24, **96 and 144**
- Change from Baseline in CD4+ lymphocyte count at Weeks 24, 48**, 96 and 144**
- Change from Baseline in CD8+ lymphocyte count and CD4+/CD8+ cell counts ratio at Weeks 24, 48**, 96, and 144**
- Incidence of disease progression (HIV-associated conditions, AIDS and death).

Section 7.3.1.3 Exploratory Efficacy Endpoints:

Previous text:

- Proportion of subjects with ~~virologic failure endpoint as per FDA snapshot category~~ by patient subgroup(s) (e.g., by age, gender, Baseline CD4+) at Week 24, 48 ~~and~~ 96 using the Snapshot algorithm for the ITT-E population
- Change from Baseline in CD4+ cell counts at Weeks 24, 48 ~~and~~ 96 by patient subgroups

Additional exploratory efficacy endpoints for subjects treated with DTG + 3TC since the Early Switch Phase, and for subjects switching in the Late Switch Phase include:

- Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 96 using the Snapshot algorithm for the ITT-E population
- Change from Baseline in CD4+ and CD8+ lymphocyte count and CD4+/CD8+ cell counts ratio at Week 96
- Incidence of disease progression (HIV associated conditions, AIDS and death) through Week 96.

Current text:

- Proportion of subjects with **plasma HIV-1 RNA <50 c/mL** by patient subgroup(s) (e.g., by age, gender, Baseline CD4+) at Week 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**, 144 and 196** by patient subgroups

Additional exploratory efficacy endpoints for subjects treated with DTG + 3TC since the Early Switch Phase, and for subjects switching in the Late Switch Phase include:

- Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week **1**96 using the Snapshot algorithm for the ITT-E population
- Change from Baseline in CD4+ and CD8+ lymphocyte count and CD4+/CD8+ cell counts ratio at Week **1**96
- Incidence of disease progression (HIV associated conditions, AIDS and death) through Week **1**96.

Section 7.4.2 Pregnancy

Added text: **Beginning after Week 96, if study visits are 24 weeks apart, the participants who are women of child bearing potential must also do a home-based urine pregnancy test approximately every 12 weeks between study visits at approximately Weeks 108, 132, 160 and 184. Site staff must contact the participants who are women of child bearing potential to remind them to complete the test and to verify and record pregnancy test results in the source documents. Site staff must complete the pregnancy status eCRF if a pregnancy occurs.**

Section 7.4.6 Table 1: Protocol Required Safety Laboratory Assessments:

Previous text:

CD8+ lymphocyte counts, percent and CD4+/CD8+ cell count ratio at Baseline and Weeks 24, 48 ~~and~~ 96

Current text:

CD8+ lymphocyte counts, percent and CD4+/CD8+ cell count ratio at Baseline and Weeks 24, 48, 96**, 144 and 196**

Section 9.2.1 Sample Size Assumptions:

Previous text:

While the targeted study size was 550 randomised subjects (from a target of 800 screened subjects), the study was over-enrolled based on an unexpected surge in recruitment in the last week of screening. ~~Based on an estimated screen failure rate of 20%,~~ a total of ~~750~~ subjects ~~are expected to be~~ randomized.

~~In this case where 750 subjects are randomized, this~~ will provide 97.~~5~~% power to show non-inferiority with the current assumptions, and non-inferiority can be declared if the actual observed treatment difference in the trial is less than or equal to 1.6%.

Current text:

While the targeted study size was 550 randomised subjects (from a target of 800 screened subjects), the study was over-enrolled based on an unexpected surge in recruitment in the last week of screening**, resulting in a** total of **743** subjects randomized.

This final sample size will provide 97.**3**% power to show non-inferiority with the current assumptions, and non-inferiority can be declared if the actual observed treatment difference in the trial is less than or equal to 1.6%.

Section 9.3.2 Analysis Data Sets

Previous text:

A secondary analysis set of data is based on subjects' responses at <50 c/mL calculated according to ~~a Missing, Switch or Discontinuation = Failure (MSDF) 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 (with the exception below) are allowed in the protocol.

Current text:

A secondary analysis set of data is based on subjects' responses at <50 c/mL calculated according to the FDA 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 (with the exception below) are allowed in the protocol.

Section 9.3.4 Interim Analysis:

Previous text: Further data cuts and analyses may be conducted as necessary to support regulatory submissions and publications. The Week 48 analysis will be primary. No adjustment for multiplicity will be made as the Week 24 analyses will be secondary.

Current text:

Week 96, Week 144 and Week 196 data cuts and analyses will be conducted. Further data cuts and analyses may be conducted as necessary to support regulatory submissions and publications. The Week 48 analysis will be primary. No adjustment for multiplicity will be made as the Week 24 analyses will be secondary**, and other analyses are**

secondary/exploratory and will occur after the primary endpoint analysis at Week 48.

Section 9.4.1 Efficacy Analyses

Removed text: ~~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 rd or rf 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 48 Snapshot analysis. Tests of homogeneity will be assessed at the one-sided 10% level of significance.~~

Previous text:

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 the responder endpoint as per FDA snapshot category, '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.~~

Changes from baseline in CD4+ lymphocyte count and in CD4+/CD8+ lymphocyte counts ratio and resistance data will be summarized~~ overall and by baseline third agent class. Details for secondary efficacy endpoints will be discussed in the RAP~~.

~~The incidence of HIV-1 disease progression (AIDS and death) will be presented.~~ The proportion of subjects with ~~Snapshot virologic failure~~ and changes from baseline in CD4+ lymphocyte count will be summarized by subgroups (e.g., age, gender, race).

Data gathered after subjects withdraw from IP 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).

Current text:

Further efficacy analyses to assess the sensitivity of the primary endpoint will be performed **and** included in the RAP.

Changes from baseline in CD4+ lymphocyte count and in CD4+/CD8+ lymphocyte counts ratio and resistance data will be summarized. **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 using the Snapshot algorithm** and changes from baseline in CD4+ lymphocyte count will be summarized by subgroups (e.g., age, gender, race).

Data gathered after subjects withdraw from IP 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, **unless otherwise stated**. 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).

Section 9.4.2 Safety Analyses:

Previous text:

Exposure to study medication, measured by the number of weeks on study drug, will be summarized 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
- Incidence of SAEs
- ~~Cumulative incidence of AEs by time to first occurrence~~
- ~~Cumulative incidence of treatment related AEs by time to first occurrence~~

The incidence and severity of treatment related AEs~~, SAEs~~ and AEs leading to withdrawal will also be assessed by baseline third agent class.

Current text:

Exposure to study medication, measured by the number of weeks on study drug, will be summarized 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
- Incidence of SAEs

The incidence and severity of treatment related AEs and AEs leading to withdrawal will also be assessed by baseline third agent class.

Section 12 References:

Added text: **Cahn P, Madero JS, Arribas J, et al. Non-inferior efficacy of dolutegravir (DTG) plus lamivudine (3TC) versus DTG plus tenofovir/emtricitabine (TDF/FTC) fixed-dose combination in antiretroviral treatment-naive adults with HIV-1 infection: 48-week results from the GEMINI studies. AIDS 2018: 22nd International AIDS Conference, Amsterdam, Netherlands, July 23-27, 2018. Abstract TUAB0106LB. http://programme.aids2018.org/Abstract/Abstract/13210**.

Section 13.3.2 Collection of Pregnancy Information:

Previous text:

- 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.

Current text:

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy **for medical reasons** will be reported as an AE or SAE.

Section 13.10.1 United Kingdom:

Previous text:

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.

The date of last study treatment administration in the UK will be determined by the completion of the Week ~~100 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 ~~Q2/Q3~~ 2018, and hence the last study treatment administration will occur by ~~Q2/~~Q3 202~~0~~. (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 Q3~~/Q4 2020~~, when the dual regimen of DTG plus 3TC is anticipated to be approved).

Current text:

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.

The date of last study treatment administration in the UK will be determined by the completion of the Week **200 visit** for the last UK subject enrolled. The last subject **was** enrolled by **June** 2018, and hence the last study treatment administration will occur by Q3 202**2**. (Note: For subjects in the UK, the **study and provision of IP** is anticipated to conclude by Q3 202**2**, **at which time** the dual regimen of DTG plus 3TC **would be available as it** is anticipated to be approved in **Q3/Q4 2020**).