TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A Phase 3b, randomised, open-label study of the antiviral activity and safety of dolutegravir compared to lopinavir/ritonavir both administered with dual nucleoside reverse transcriptase inhibitor therapy in HIV-1 infected adult subjects with treatment failure on first line therapy

Compound Number: GSK1349572

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Author(s): PPD
PPD
PPD
PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2013N172672_00	2014-APR-01	Original
2013N172672_01	2014-APR-30	Amendment No. 1
This amendment includes the removal of exclusion criterion 18 (subject has creatinine clearance of <50 mL/min via the CKD-EPI method). Allergic reaction criteria are referred to in Section 4.5 "Withdrawal criteria". Furthermore, the sequence of administration of the HIVTSQ status and change versions has been amended. Other minor clarifications and corrections have been incorporated.		
2013N172672_02	2017-APR-19	Amendment No. 2
This amendment includes a change in the study design giving subjects originally randomised to the LPV/RTV arm the option to switch to the DTG arm prior to study completion. This change is being implemented following an IDMC recommendation to discontinue the LPV/RTV arm. Revisions to the Suicidality Monitoring and data analysis sections and edits to the Time and Events Table are also included. Other minor clarifications and corrections have been incorporated.		
2013N172672_03	2018-JUN-19	Amendment No. 3
This amendment includes changes 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. The changes include updates to the Risk Assessment and acceptable methods of contraception, and a reminder that females of childbearing potential who change their minds and desire to be pregnant or who do not wish to comply with the approved pregnancy avoidance methods, should be withdrawn from the study. Investigators are also reminded to check at every visit that females of childbearing potential are avoiding pregnancy. Other minor clarifications and corrections have been incorporated.		

SPONSOR SIGNATORY

PPD

PPD

Kimberly Y. Smit[redacted] PPD
Vice President and He[redacted]al
Research and Medical [redacted]
ViiV Healthcare

Date

PPD

MEDICAL MONITOR /SPONSOR INFORMATION PAGE

Clinical Study Identifier: 200304

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

Sponsor Name and Legal Registered Address (excluding US):

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

US IND Sponsor Name and Legal Registered Address:

ViiV Healthcare Company
Five Moore Drive
P.O. 13398
Research Triangle Park, NC 27709-3398, USA
Telephone: + 1 919 483 2100

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

Medical Monitor Contact Information and Serious Adverse Events (SAE) Contact Information:

PPD , MD, PhD
ViiV Healthcare
980 Great West Road
Brentford,
Middlesex, TW8 9GS
UK
Mobile: +PPD
PPD

Secondary contact:

PPD , MD
ViiV Healthcare
5 Moore Drive
Research Triangle Park, NC 27709
USA
Mobile: +PPD
PPD

Regulatory Agency Identifying Number(s):

EudraCT: 2014-001057-17

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 200304

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

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

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

Investigator Name:		
Investigator Address:		
Investigator Phone Number:		
Investigator Signature		Date

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LIST OF ABBREVIATIONS

3TC	Lamivudine, EPIVIR
AE	Adverse event
ABC	Abacavir, ZIAGEN
ABC/3TC	Abacavir/Lamivudine, EPZICOM, KIVEXA
ACTG	AIDS Clinical Trials Group
AIDS	Acquired immune deficiency syndrome
ALT	Alanine aminotransferase
anti-HBc	Antibody to hepatitis B core antigen
anti-HCV	Antibody to hepatitis C virus
APAP	Acetaminophen
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
ATV	Atazanavir, Reyataz
BUN	Blood urea nitrogen
c/mL	Copies/millilitre
CD4+	Helper-inducer T-lymphocyte having surface antigen CD4 (cluster of differentiation 4)
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMH	Cochran-Mantel-Haenszel
COBI	Cobicistat, Tybost
CPK	Creatine phosphokinase
CRF/eCRF	Case report form/electronic case report form
CSR	Clinical study report
C-SSRS	Columbia Suicidality Severity Rating Scale
d4T	Stavudine
DAIDS	Division of Acquired Immune Deficiency Syndrome
DILI	Drug induced liver injury
DNA	Deoxyribonucleic acid
DTG	Dolutegravir
ECG	Electrocardiograph
EFV	Efavirenz
ELV	Elvitegravir
EMA	European Medicines Agency
FDA	Food and Drug Administration
FTC	Emtricitabine
GCP	Good clinical practice
GCSP	Global Clinical Safety and Pharmacovigilance
GFR	Glomerular filtration rate
GI	Gastrointestinal
GSK	GlaxoSmithKline
GSRS	Gastrointestinal Symptom Rating Scale
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus

HDL	High density lipoprotein
HDPE	High density polyethylene
HIV-1	Human immunodeficiency virus type 1
HIVTSQ	HIV Treatment Satisfaction Questionnaire
HIVTSQs	HIVTSQ status version
HIVTSQc	HIVTSQ change version
HLA	Human leukocyte antigen
HSR	Hypersensitivity reaction
IB	Investigator's brochure
ICH	International Conference on Harmonization
IDMC	Independent data monitoring committee
IEC	Independent ethics committee
IgM	Immunoglobulin M
INI	Integrase inhibitor
IP	Investigational product
IRB	Institutional review board
IRIS	Immune reconstitution inflammatory syndrome
ITT	Intent to Treat
IUD	Intrauterine device
IVRS	Interactive voice recognition system
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LLOD	Lower limit of detection
LPV/RTV	Lopinavir/ritonavir, Kaletra
LSLV	Last subject's last visit
MCV	Mean corpuscular volume
MMAS-8	Morisky 8-Item Medication Adherence Scale
MSDF	Missing, switch or discontinuation = failure
MSDS	Material safety data sheet
mg	Milligram
mL	Millilitre
NCEP	National Cholesterol Education Program
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
OC	Observed case
OCT2	Organic cation transporter 2
PBMC	Peripheral blood mononuclear cell
PDVF	Protocol defined virologic failure
PGx	Pharmacogenetic
PI	Protease inhibitor
PK	Pharmacokinetic
Pol	Polymerase
PP	Per protocol
PRO	Protease
PSRAE	Possible suicidality related adverse event
QT_C	Corrected QT interval
RAL	Raltegravir, Isentress
RAP	Reporting and analysis plan

RBC	Red blood cells
RNA	Ribonucleic acid
RT	Reverse transcriptase
RTV	Ritonavir, Norvir
SAE	Serious adverse event
SDAC	Statistics Data Analysis Centre
SJS	Stevens Johnson Syndrome
SPM	Study procedure manual
STR	Single tablet regimen
TAM	Thymidine analogue mutation
TC	Total cholesterol
TEN	Toxic epidermal necrolysis
TDF	Tenofovir disoproxil fumarate, Viread
ULN	Upper limit of normal
US	United States
VSLC	ViiV Safety and Labeling Committee
WBC	White blood cells
WHO	World Health Organization

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Phenosense
Quest Diagnostics
Reyataz (atazanavir)
Stribild (elvitegravir/cobicistat/ tenofovir/emtricitabine)
Tybost (cobicistat)
Vitekta (elvitegravir)

PROTOCOL SUMMARY

Rationale

Access to antiretroviral therapy (ART) in low-income and middle-income countries has been scaled-up effectively over recent years. Despite these advances, the number of patients failing on their first-line regimen is increasing thereby requiring a switch to second-line treatment to reduce accumulation of drug-resistance mutations, disease progression, human immunodeficiency virus (HIV) transmission, and death. Publicly funded programmes tend to follow World Health Organization (WHO) guidelines to use a non-nucleoside reverse transcriptase inhibitor (NNRTI) combined with two nucleoside reverse transcriptase inhibitors (NRTIs) for first-line ART; however, there is a need for further data on the best treatment options for people with HIV-1 who have virological failure with this first-line regimen. WHO guidelines recommend second-line antiretroviral therapy for adults consisting of two NRTIs + a ritonavir-boosted protease inhibitor (PI); atazanavir plus ritonavir (ATV+RTV) or lopinavir (LPV)/RTV are the preferred boosted PI options.

Several studies have been conducted or are currently underway to investigate novel treatment strategies (i.e. NRTI-sparing regimens) in patients requiring second-line ART. There are currently no studies ongoing to explore the potential option of PI-sparing second-line ART. This strategy, especially with the availability of agents from non-PI classes with a high barrier to resistance, may have some advantages over PI-based regimens, particularly from a safety and tolerability perspective. This study compares a second-line regimen of dolutegravir (DTG) plus two NRTIs with a WHO-recommended regimen of LPV/RTV plus two NRTIs.

Objectives

Primary Objective

- To demonstrate non-inferior antiviral activity at 48 weeks of a DTG containing regimen (DTG 50 mg once daily + two NRTIs) compared to a WHO-recommended standard of care regimen for second line treatment, LPV/RTV + two NRTIs, in HIV-1 infected patients failing first line therapy.

Secondary Objectives

- To demonstrate non-inferior antiviral activity at 24 weeks of a DTG containing regimen (DTG 50 mg once daily + two NRTIs) compared to a recommended WHO standard of care regimen for second line treatment, LPV/RTV + two NRTIs, in HIV-1 infected patients failing first line therapy;

- To evaluate the antiviral and immunological activity and incidence of disease progression (HIV-associated conditions, AIDS and death) of DTG compared to LPV/RTV over time;

- To assess the development of viral resistance in subjects meeting confirmed virologic withdrawal criteria;

- To evaluate the safety, tolerability, and laboratory parameters of DTG compared to LPV/RTV over time;

- To compare the effects of DTG and LPV/RTV on fasting lipids over time;

- To compare the effects of DTG and LPV/RTV on the occurrence of gastrointestinal adverse events over time;

- To compare the change in gastrointestinal symptom rating score for subjects treated with DTG and LPV/RTV over time;

- To compare the satisfaction with treatment of patients with DTG compared to the LPV/RTV over time;

- To compare patients' adherence with DTG compared to the LPV/RTV over time;

- To evaluate the effect of patient demographics and baseline characteristics (e.g. demographic factors, HIV-1 subtype, baseline CD4+ cell count) on response to DTG compared to LPV/RTV over time.

Study Design

This study is a Phase IIIb, randomised, open-label, active-controlled, multicenter, parallel group, non-inferiority study. Approximately 612 adult patients with confirmed virologic failure (HIV-1 RNA ≥400 copies/mL [c/mL] on two occasions) on their first antiretroviral regimen consisting of one NNRTI + two NRTIs will be recruited. Subjects will be randomised 1:1 to receive DTG 50 mg once daily or LPV/RTV (800/200 mg once daily or 400/100 mg twice daily, in accordance with investigator decision and local label), each added to an investigator selected background regimen consisting of two NRTIs. The background regimen shall be constructed by the investigator based on viral resistance testing at Screening and be composed of at least one fully active NRTI plus one more NRTI which may or may not be active. In consultation with the medical monitor, lamivudine (3TC) may be added as a third NRTI to a dual-NRTI background regimen in subjects with chronic HBV infection and evidence of HIV resistance to 3TC (e.g. M184V). 3TC cannot be added to regimens that include FTC.

Randomisation will be stratified by Screening plasma HIV-1 RNA (≤100,000 c/mL or >100,000 c/mL) and number of fully active NRTIs in the investigator selected study background regimen (2 versus <2).

The study will comprise a Screening Phase (approximately 28 to 42 days), a Randomised Phase (Day 1 to Week 48 plus a 4-week treatment extension), and a Continuation Phase.

The 4-week treatment extension up to Week 52 within the Randomised Phase is 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 primary efficacy endpoint corresponds

to viral load measurements collected within a ± 6 week window around the Week 48 visit (including data from the Week 52 visit), as per the FDA's Snapshot algorithm, and for this reason, the primary analysis is denoted as occurring at Week 48 with the understanding that data from the Week 52 visit may be included.

The primary analysis at Week 48 will take place after the last subject completes 52 weeks on therapy (Day 1 to Week 48 plus a 4-week treatment extension). An interim analysis and data cut will be conducted after the last subject completes 24 weeks on therapy, with the intent to provide an earlier assessment of efficacy to inform the Sponsor and clinicians. A switch from LPV/RTV 800/200 mg once daily to 400/100 mg twice daily and the opposite switch and a single change of one of the background NRTIs for toxicity or tolerability management is allowed. Any NRTI change must ensure a fully active NRTI is still present based on Screening resistance testing. A switch from 3TC to emtricitabine (FTC) (or vice versa) will not be considered a background NRTI change and is permitted. No other dose reductions, modifications in dosage, or changes in the frequency of dosing will be allowed in this study.

Subjects randomised to receive DTG who successfully complete 52 weeks of treatment will continue to have access to DTG (Continuation Phase) until it is either locally approved and commercial supplies are available to patients (e.g. through public health services), the patient no longer derives clinical benefit, or the patient meets a protocol-defined reason for discontinuation. Subjects randomised to the LPV/RTV arm will receive LPV/RTV through their Week 48 visit and during the 4-week treatment extension only, after which they will complete the study and will need to have alternate arrangements in place to access antiretroviral medication.

An IDMC has been instituted to perform periodic reviews of the accumulating data to ensure that subjects are not being sub-optimally treated. **The IDMC completed two of the three pre-planned analyses. Prior to interim analysis #3, the IDMC conducted an ad-hoc review of trial data and observed significant, clinically relevant differences between treatment arms in favour of DTG. The IDMC recommended to the sponsor that the LPV/RTV treatment arm be discontinued and subjects currently receiving LPV/RTV in the study be switched to a regimen with DTG as the third drug, if considered appropriate by the Investigator. As per Protocol Amendment No. 2, subjects randomised to the LPV/RTV arm will either (i) continue receiving LPV/RTV and complete the study after the 4-week treatment extension (see above), or (ii) switch to the DTG arm prior to study completion at Week 52 and continue to have access to DTG in the Continuation Phase until DTG is either locally approved and commercial supplies are available to patients (e.g. through public health services), the patient no longer derives clinical benefit, or the patient meets a protocol-defined reason for discontinuation. Subjects originally randomised to DTG and receiving DTG in the Randomised Phase or in the Continuation Phase are not affected by this IDMC recommendation and Protocol Amendment No. 2.**

Study Endpoints/Assessments

The primary endpoint for this study will be the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm (Missing, Switch or Discontinuation = Failure) for the intent-to-treat exposed (ITT-E) population.

Secondary efficacy endpoints will include:

- Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 24 using the Snapshot algorithm;
- Proportion of subjects with plasma HIV-1 RNA <400 c/mL at Weeks 24 and 48 using the Snapshot algorithm;
- Proportion of subjects without virologic or tolerability failure by Weeks 24 and 48, where failure equals treatment-related discontinuation (meeting confirmed virologic withdrawal criteria, treatment-related adverse event, safety stopping criteria, and lack of efficacy);
- Time to viral suppression (HIV-1 RNA <50 c/mL);
- Absolute values and changes from Baseline in CD4+ cell counts at Weeks 24 and 48;
- Incidence of disease progression (HIV-associated conditions, AIDS and death).

Safety endpoints will include:

- Incidence and severity of AEs and laboratory abnormalities;
- Absolute values and changes over time in laboratory parameters;
- Change from Baseline in fasting LDL cholesterol at Weeks 24 and 48;
- Change from Baseline in fasting TC/HDL ratio at Weeks 24 and 48;
- Incidence of maximum post-Baseline emergent Grade 2 or greater laboratory abnormalities in fasting LDL cholesterol by Weeks 24 and 48;
- Incidence of maximum post-Baseline emergent Grade 2 or greater drug-related diarrhoea by Weeks 24 and 48;
- Proportion of subjects who discontinue treatment due to AEs.

Health outcome endpoints will include:

- Change from Baseline, using the Gastrointestinal Symptom Rating Scale (GSRS), at Week 4, Week 24, and Week 48;
- Change from Baseline in treatment satisfaction, using the HIV-Treatment Satisfaction Questionnaire (HIVTSQ), at Weeks 4, 24, and 48;
- Change from Baseline in adherence with treatment, using the Morisky Medication Adherence eight item scale (MMAS-8), at Weeks 4, 24 and 48.

Virology endpoints will include:

- Incidence of treatment-emergent genotypic and phenotypic resistance to DTG, LPV/RTV and other on-study ART in subjects meeting confirmed virologic withdrawal criteria.

1. INTRODUCTION

1.1. Background

Integrase inhibitors (INIs) are a relatively new class of antiretroviral drugs designed to block the action of the integrase viral enzyme, which catalyzes several key steps in the human immunodeficiency virus type 1 (HIV-1) life cycle and is responsible for insertion of the viral genome into the deoxyribonucleic acid (DNA) of the host cell. Since integration is an essential step in retroviral replication, it is an attractive target for HIV therapy. The first HIV INI, raltegravir (RAL) [Isentress Package Insert, 2013; Isentress, Summary of Product Characteristics, 2013], was approved by the United States (US) Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2007. Elvitegravir (ELV), another HIV INI, was approved by the US FDA in 2012 and by the EMA in 2013 as part of a single tablet regimen (STR) with cobicistat (COBI), tenofovir (TDF), and emtricitabine (FTC) [Stribild Package Insert, 2013; Stribild Summary of Product Characteristics, 2013] as well as for use as an individual drug by the EMA in November 2013 [Vitekta Summary of Product Characteristics, 2013].

Dolutegravir (DTG) is a next-generation INI with low-moderate inter-subject pharmacokinetic variability, a predictable exposure-response relationship and a 14-hour plasma half-life that supports once daily dosing without the need for the PK boosters that are required with ELV. DTG was approved by the US FDA in August 2013 and by the EMA in January 2014 [TIVICAY Package Insert, 2017; TIVICAY Summary of Product Characteristics, 2017].

To date, the efficacy, pharmacokinetics, safety and drug interaction potential of DTG have been evaluated in an extensive program of Phase I to III clinical trials. Data are summarised in the Investigator's Brochure (IB [GlaxoSmithKline Document Number .RM2007/00683/11]; IB Supplement 01 [GlaxoSmithKline Document Number [2017N352880_00]; IB Supplement 02 [GlaxoSmithKline Document Number 2017N352880_01]). In both antiretroviral therapy (ART)-naïve and ART-experienced (INI- naïve) patients, the safety profile for DTG 50 mg once daily was comparable to RAL and darunavir plus ritonavir (DRV+RTV) and generally favourable to the STR of efavirenz (EFV)/TDF/FTC (Atripla) (studies ING113086 [SPRING-2], ING111762 [SAILING], ING114915 [FLAMINGO] and ING114467 [SINGLE]). The most frequently observed AEs across patient populations were diarrhoea, nausea, and headache, which were generally Grade 1 or 2 in severity, and typically did not lead to discontinuation from studies. With regards to antiviral efficacy, in treatment-naïve HIV-infected adult subjects, DTG 50 mg once daily was shown to be efficacious, and non-inferior to RAL in combination with a dual nucleoside reverse transcriptase inhibitor (NRTI) background regimen [SPRING-2]. In study ING114915 [FLAMINGO], virologic suppression (HIV-1 RNA <50 copies/mL [c/mL]) in the DTG arm was statistically superior to the DRV+RTV arm at Week 48. DTG used in combination with abacavir/lamivudine (ABC/3TC, EPZICOM/KIVEXA™) was also shown to be superior to EFV/TDF/FTC at Week 48, a result driven by better tolerability of the DTG-based regimen [SINGLE]. DTG also demonstrated superior virologic suppression (HIV-1 RNA <50 c/mL) compared with RAL in combination with investigator selected two drug background regimen for INI-naïve treatment experienced patients in the Phase III study

ING111762 [SAILING]. Finally, DTG also showed good efficacy in ART-experienced patients with INI resistance in ING112574 [VIKING-3].

Furthermore, DTG 50 mg once daily may have a higher barrier to resistance in INI-naive patients, as suggested in the treatment-experienced (INI-naive) SAILING study where significantly fewer virologic failures with INI resistance were observed when compared with RAL. Data from Phase III studies [SPRING-2, SINGLE and FLAMINGO] in treatment-naive subjects are also supportive of a high barrier to resistance.

Access to ART in low-income and middle-income countries has been scaled-up effectively over recent years reaching 8 million people by the end of 2011 [UNAIDS, 2012]. Despite these advances, the number of patients failing on their first-line regimen is increasing thereby requiring a switch to second-line treatment to reduce accumulation of drug-resistance mutations, disease progression, HIV transmission, and death [WHO, 2011]. Publicly funded programmes tend to follow WHO guidelines to use a non-nucleoside reverse transcriptase inhibitor (NNRTI) combined with two NRTIs for first-line ART [WHO, 2013; WHO, 2016]; however, there is a need for further data on the best treatment options for people with HIV-1 who have virological failure with this first-line regimen. WHO guidelines recommend second-line ART for adults consisting of two NRTIs + a ritonavir-boosted protease inhibitor (PI) with atazanavir (ATV)+RTV or LPV/RTV as the preferred boosted PI options [WHO, 2013; WHO, 2016].

In many low to middle income countries, LPV/RTV is the most widely used PI for second-line ART although the use of ATV+RTV is increasing. LPV/RTV is associated with lipid and gastrointestinal side effects [Molina, 2008; Ortiz, 2008; Mills, 2009]. PIs have also been associated with increased risk of decreased bone mineral density, renal impairment and cardiovascular disease, although the pathogenesis of complications in each organ is multi-factorial and complex [Brown, 2006; Ryom, 2013; Currier, 2008].

A sequence of second-line NRTI options are recommended based on the likely activity of each NRTI against predicted resistance to ZDV/stavudine (d4T), 3TC/FTC and/or TDF when used in first line treatment [WHO, 2013; WHO, 2016]. This strategy is particularly useful in settings where resistance testing is not available. Depending on the development of resistance and taking into account local standard of care as well as drug availability, other NRTIs such as abacavir (ABC) may be considered in other settings.

Several studies have been conducted or are currently underway to investigate novel treatment strategies (i.e. NRTI-sparing regimens) in patients requiring second-line ART. The SECOND-LINE Study is a randomised clinical trial, which has demonstrated that the efficacy of a novel dual-treatment approach combining LPV/RTV with the integrase inhibitor (INI) raltegravir (RAL) was non-inferior to a WHO-recommended second-line treatment regimen of LPV/RTV plus two or three NRTIs over 96 weeks [SECOND-LINE Study Group, 2013]. Findings from this study show that the WHO-recommended second-line treatment is an efficacious rescue regimen and also provide evidence for an alternative NRTI-sparing approach. In the Europe-Africa Research Network for Evaluation of Second-line Therapy (EARNEST) Trial, a second-line regimen consisting of LPV/RTV (400 mg/100 mg twice daily) plus two NRTIs has also led to good

outcomes; the NRTI-sparing regimen with LPV/RTV plus RAL evaluated in the study was not superior, and LPV/RTV monotherapy was inferior [Paton, 2013].

The HIV STAR study showed that in patients failing initial therapy on an NNRTI + two NRTI regimen, treatment with LPV/RTV monotherapy led to a significantly lower proportion of patients achieving HIV RNA <50 c/mL at Week 48 compared to LPV/RTV + TDF/FTC treatment [Bunupuradah, 2012].

The 2LADY study (ANRS 12169) is a clinical trial evaluating three different second-line combinations (LPV/RTV + TDF/FTC, LPV/RTV + ABC + ddI, and DRV + RTV + TDF/FTC) in Sub-Saharan Africa enrolling patients on ART who meet the WHO immunologic or clinical failure criteria. After undergoing a month of adherence support, patients are randomised to one of the three arms of the study unless they show a significant decrease of viral load and are kept on first-line therapy [Mazoyer, 2010]. The 96-week SELECT Study (A5273) compares, like the SECOND-LINE Study, two second-line regimens, LPV/RTV with RAL versus LPV/RTV plus two or three NRTIs [ACTG, 2014].

1.2. Rationale

There are currently no studies ongoing to explore the potential option of PI-sparing second-line ART. This strategy, especially with the availability of agents from non-PI classes with a high barrier to resistance, may have some advantages over PI-based regimens, particularly from a safety and tolerability perspective. This study compares a second-line regimen of DTG plus two NRTIs with a WHO-recommended regimen of LPV/RTV with two NRTIs.

1.3. Benefit:Risk Assessment

Summaries of DTG can be found in the IB [GlaxoSmithKline Document Number RM2007/00683/11, GlaxoSmithKline Document Number 2017N352880_00, and GlaxoSmithKline Document Number 2017N352880_01]. The following section outlines the risk assessment and mitigation strategy for DTG in this protocol. Where available, the approved country product label should be referenced.

For LPV/RTV and background NRTIs, the approved country product labels should be referenced. The comparator regimen, LPV/RTV plus two NRTIs, is a preferred treatment regimen for HIV-infected patients requiring second-line ART according to current WHO guidelines [WHO, 2013; WHO, 2016].

1.3.1. Risk Assessment

All medications have AE profiles that must be assessed prior to use, allowing for an appropriate risk/benefit assessment. Considerations when using DTG are as follows:

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy[1]
Investigational Product (IP) [DTG] Refer to IB for additional information on DTG		
Hypersensitivity and rash	HSR has been observed uncommonly with DTG. Rash was commonly reported in DTG Phase IIb/III clinical trials; episodes were generally mild to moderate in intensity; no episodes of severe rash, such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and erythema multiforme were reported.	Subjects with history of allergy/sensitivity to any of the study drugs are excluded (Section 4.3). Specific/detailed toxicity management guidance is provided for HSR (Section 6.4.4.6) and rash (Section 6.4.4.7). The subject informed consent form includes information on this risk and the actions subjects should take in the event of an HSR or associated signs and symptoms.
Drug induced liver injury (DILI) and other clinically significant liver chemistry elevations	Non-clinical data suggested a possible, albeit low, risk for hepatobiliary toxicity with DTG. Drug-related hepatitis is considered an uncommon risk for 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.	Subjects meeting either of the following criteria during the screening period are excluded from participating (Section 4.3). • Alanine aminotransferase (ALT) ≥5 times the upper limit of normal (ULN) or ALT ≥3xULN and bilirubin ≥1.5xULN (with >35% direct bilirubin) • Subjects with an anticipated need for hepatitis C virus (HCV) therapy during the Randomised Phase (Day 1 to Week 48 plus a 4-week treatment extension) Investigators should consult current treatment guidelines when considering choice of NRTIs for subjects with chronic HBV infection. Additional treatment considerations should be guided by local treatment guidelines. Adequate HBV therapy must be administered to subjects with chronic HBV infection (see Section 6.2.3). Specific/detailed liver stopping criteria and toxicity management guidance is provided for suspected DILI or other clinically significant liver chemistry elevations (Section 6.4.4.1).

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy[1]
Investigational Product (IP) [DTG] Refer to IB for additional information on 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 (OCT2) transporter, resulting in potentially life-threatening toxicity.	The co-administration of DTG with dofetilide or pilsicainide is prohibited in the study (Section 5.6.3).
Gastrointestinal (GI) intolerance	Non-clinical studies showed upper and lower GI toxicity, including vomiting, diarrhoea and gastric erosions observed in monkey toxicology studies (thought to be related to local and not systemic toxicity). Mild to moderate GI intolerance (mainly diarrhoea and nausea) is associated with DTG treatment in a small proportion of subjects; however there were no indications of an increased risk for peptic ulcers or serious erosions.	Routine monitoring of GI symptoms will be performed.
Renal function	Mild elevations of creatinine have been observed with DTG which are related to a likely benign effect on creatinine secretion with blockade of OCT2 receptor. DTG has been shown to have no significant effect on glomerular filtration rate (GFR) or effective renal plasma flow.	Specific/detailed toxicity management guidance is provided for subjects who develop a decline in renal function (Section 6.4.4.5).
Psychiatric disorders	Psychiatric disorders including suicide ideation and behaviours are common in HIV-infected patients. The psychiatric profile for DTG (including suicidality, depression, bipolar and hypomania, anxiety and abnormal dreams) was similar to RAL- or favourable compared with EFV-based regimens. The reporting rate for insomnia was statistically higher for blinded DTG+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, poses a significant suicidality risk, are excluded from participating (Section 4.3). Because of the elevated risk in the HIV- infected population, treatment emergent assessment of suicidality will be monitored during this study. Investigators are advised to consider mental health consultation or referral for subjects who experience signs of suicidal ideation or behaviour (Section 6.4.10).
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 6.4.4.4).

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy[1]
Investigational Product (IP) [DTG] Refer to IB for additional information on DTG		
Increased occurrence of Immune reconstitution inflammatory syndrome (IRIS)	With rapid HIV-1 RNA decline and early recovery of CD4+ cell counts there could theoretically, be an increase in cases of IRIS. Based on medical adjudication of IRIS-like events in ING111762, ART-experienced (INI-naïve) subjects with hepatitis B or C virus co-infection receiving DTG may be at greater risk for IRIS than those receiving RAL, due to improved HIV virologic and immunologic responses with DTG compared to RAL, and withdrawal (or lack) of HBV active therapy in HIV/HBV co-infected subjects.	Subjects will have frequent liver chemistry monitoring. Robust liver chemistry stopping criteria and liver event follow up assessments are included. Investigators are expected to follow local HBV and HCV treatment guidelines (see Section 6.2.3. and Section 6.2.4).
Functional monotherapy with DTG or LPV/RTV	Subjects are at risk of receiving functional monotherapy with their second-line regimen due to recycling of NRTIs to which their virus has already developed partial or full resistance.	The study requires that eligible subjects receive at least one fully active NRTI within the background regimen based on Screening genotypic resistance testing results as well as prior treatment history and, if available, any previous genotypic (and phenotypic) results showing resistance to an agent; a lack of resistance in previous results does not confirm susceptibility.
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, and, if she is a female of childbearing potential, agrees to follow one of the options for prevention of pregnancy listed in the Inclusion Criterion 2 (see Section 4.2) during treatment with study drug and until at least 2 weeks after the last dose of study medication. 2. Women who become pregnant, or who desire to be pregnant while in the study will have study treatment discontinued and be withdrawn from the study. 3. Females of childbearing potential are reminded re: pregnancy avoidance and adherence to contraception requirements at every study visit. 4. Pregnancy status is monitored at every study visit.

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

1.3.2. Benefit Assessment

DTG is conveniently dosed once daily, without need for a PK booster or food/fluid restrictions, and with limited safety implications resulting from theoretical or actual drug: drug interactions compared to other antiretroviral agents (including EFV and those requiring a PK booster).

The safety profile for DTG 50 mg once daily was comparable to RAL and DRV+RTV and generally favourable to the EFV/TDF/FTC STR (Atripla) in both ART-naïve and ART-experienced (INI-naïve) patients (studies ING113086 [SPRING-2], ING111762 [SAILING], ING114915 [FLAMINGO] and ING114467 [SINGLE]). The most frequently observed AEs across patient populations were diarrhoea, nausea, and headache, which were generally Grade 1 or 2 in severity, and typically did not lead to discontinuation from studies. With regards to antiviral efficacy, in treatment-naïve HIV-infected adult subjects, DTG 50 mg once daily was shown to be non-inferior to RAL in combination with a dual NRTI background regimen [SPRING-2]. In study ING114915 [FLAMINGO], virologic suppression (HIV-1 RNA <50 c/mL) in the DTG arm (90%) was statistically superior to the DRV+RTV arm (83%) at Week 48. When used in combination with ABC/3TC, DTG was shown to be superior to EFV/TDF/FTC, a result driven by better tolerability of the DTG based regimen [SINGLE]. In study ING111762 [SAILING], 71% of in INI-naïve ART-experienced patients receiving DTG achieved undetectable viral load (<50 c/mL) compared with 64% of those taking RAL at Week 48, reaching the threshold for statistical superiority [Cahn, 2013]. Excellent antiviral activity of DTG in patients with INI resistance was demonstrated in study ING112574 [VIKING-3].

Furthermore, DTG 50 mg once daily may have a higher barrier to resistance than RAL in INI-naïve patients.

Uncertainty remains about the best treatment for HIV-1 infected patients who have virological failure with first-line ART of an NNRTI + two NRTIs. This study compares a new PI-sparing second-line regimen with a WHO-recommended regimen. This strategy, especially with the availability of agents from non-PI classes with a high barrier to resistance, may have some advantages over PI-based regimens, particularly from a safety and tolerability perspective.

The study requires that eligible subjects receive at least one fully active NRTI within the background regimen based on Screening genotypic resistance testing results. Previous genotypic (and phenotypic) results can provide evidence of resistance but cannot provide proof of a lack of resistance.

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

1.3.2.1. Analysis of subjects receiving DTG + 1-2 NRTIs in SAILING

In order to inform the study design, an exploratory analysis of subjects receiving DTG + 1-2 NRTIs in ING111762 (SAILING) was conducted. SAILING compared DTG and

raltegravir (RAL) in combination with up to two investigator selected background antiretroviral drugs (at least 1 being fully active) in antiretroviral therapy-experienced, integrase inhibitor-naïve adults with ongoing virologic failure and at least two-class drug resistance [Cahn, 2013]. Of the 715 subjects randomised, 32 subjects in each arm received an NRTI-based background regimen; all subjects received two NRTIs except for one subject in the DTG arm receiving only one NRTI.

None of the 32 subjects in the DTG arm experienced protocol defined virologic failure (PDVF) by Week 48, including no cases of virologic failure in 13 subjects receiving less than 2 fully active NRTIs by phenotype (12 received one fully active NRTI and 1 received two inactive NRTIs). In the RAL arm, 7/32 (22%) of subjects experienced PDVF by Week 48, of which 4/13 (31%) experienced failure with 1 fully active NRTI and 3/19 (16%) failed with 2 fully active NRTIs. Of the 13 subjects who had the M184V mutation detected at baseline and received DTG + 3TC/FTC + a second NRTI, none met PDVF criteria, including 10 subjects for whom the second NRTI was active (by phenotype) and 3 subjects with 2 or more thymidine analogue mutations (TAMs). Four of 12 subjects (33%) who received RAL + 3TC/FTC + a second NRTI in the setting of baseline M184V experienced PDVF, despite the fact that the second NRTI was active by phenotype in all these cases.

Based on this exploratory analysis, DTG + two NRTIs appears to have good activity through 48 weeks in treatment-experienced patients who are experiencing virologic failure when at least one of NRTIs was fully active by phenotype. However, the sample size is small, and an increased risk of virologic failure in subjects receiving DTG with less than two fully active NRTIs cannot be ruled out based on these data alone.

1.3.3. Overall Benefit:Risk Conclusion

Taking into account the measures taken to minimise risk to subjects participating in this study, the potential risks identified in association with DTG are justified by the anticipated benefits that may be afforded to HIV-1 infected adults with treatment failure on first line therapy.

2. OBJECTIVES

Primary Objective

- To demonstrate non-inferior antiviral activity at 48 weeks of a DTG containing regimen (DTG 50 mg once daily + two NRTIs) compared to a WHO-recommended standard of care regimen for second line treatment, LPV/RTV + two NRTIs, in HIV-1 infected patients failing first line therapy.

Secondary Objectives

- To demonstrate non-inferior antiviral activity at 24 weeks of a DTG containing regimen (DTG 50 mg once daily + two NRTIs) compared to a recommended WHO standard of care regimen for second line treatment, LPV/RTV + two NRTIs, in HIV-1 infected patients failing first line therapy;

- To evaluate the antiviral and immunological activity and incidence of disease progression (HIV-associated conditions, AIDS and death) of DTG compared to LPV/RTV over time;
- To assess the development of viral resistance in subjects meeting confirmed virologic withdrawal criteria;
- To evaluate the safety, tolerability, and laboratory parameters of DTG compared to LPV/RTV over time;
- To compare the effects of DTG and LPV/RTV on fasting lipids over time;
- To compare the effects of DTG and LPV/RTV on the occurrence of gastrointestinal adverse events over time;
- To compare the change in gastrointestinal symptom rating score for subjects treated with DTG and LPV/RTV over time;
- To compare the satisfaction with treatment of patients with DTG compared to the LPV/RTV over time;
- To compare patients' adherence with DTG compared to the LPV/RTV over time;
- To evaluate the effect of patient demographics and baseline characteristics (e.g. demographic factors, HIV-1 subtype, baseline CD4+ cell count) on response to DTG compared to LPV/RTV over time.

3. INVESTIGATIONAL PLAN

3.1. Study Design

This study is a Phase IIIb, randomised, open-label, active-controlled, multicenter, parallel group, non-inferiority study.

Approximately 612 adult patients with confirmed virologic failure (HIV-1 RNA ≥400 c/mL on two occasions) on their first antiretroviral regimen consisting of one NNRTI + two NRTIs will be recruited.

Subjects will be randomised 1:1 to receive DTG 50 mg once daily or LPV/RTV (800/200 mg once daily or 400/100 mg twice daily, in accordance with investigator decision and local label), each added to an investigator selected background regimen consisting of two NRTIs with at least one fully active NRTI (see Section 5.1.3). In consultation with the medical monitor, 3TC may be added as a third NRTI to a dual-NRTI background regimen in subjects with chronic HBV infection and evidence of HIV resistance to 3TC (e.g. M184V) (see Section 6.2.3).

The primary analysis at Week 48 will take place after the last subject completes 52 weeks on therapy (Day 1 to Week 48 plus a 4-week treatment extension). An interim analysis and data cut will be conducted after the last subject completes 24 weeks on therapy, with

the intent to provide an earlier assessment of efficacy to inform the Sponsor and clinicians. A switch from LPV/RTV 800/200 mg once daily to 400/100 mg twice daily and the opposite switch and a single change of one of the background NRTIs for toxicity or tolerability management is allowed. Any NRTI change must ensure a fully active NRTI is still present based on Screening resistance testing. A switch from 3TC to FTC (or vice versa) will not be considered a background NRTI change and is permitted. No other dose reductions, modifications in dosage, or changes in the frequency of dosing will be allowed in this study.

An IDMC has been instituted to perform periodic reviews of the accumulating data to ensure that subjects are not being sub-optimally treated. **The IDMC completed the first two of the three pre-planned analyses (see Section 8.3.4.2). Prior to the third interim analysis, the IDMC conducted an ad hoc review of trial data and the IDMC observed significant, clinically relevant differences between treatment arms in favour of DTG. The IDMC recommended to the sponsor that the LPV/RTV treatment arm be discontinued and subjects currently receiving LPV/RTV in the study be switched to a regimen with DTG as the third drug, if considered appropriate by the Investigator.**

Assuming a true response rate of 70% for both DTG and LPV/r arms, the study requires 306 subjects per arm to have 90% power with a 12% non-inferiority margin and a one-sided 2.5% significance level (see Section 8.2.1).

The study design is summarised in Figure 1 and comprises the following Phases:

Screening Period

Randomisation may occur as soon as all Screening procedures have been completed and results are available and on file. Subjects will participate in a Screening period of up to 28 days, which may be extended to 42 days to ensure eligibility (e.g. receipt of final Screening laboratory results) and scheduling. Eligibility criteria must be fulfilled by current resistance testing, i.e. Screening results.

Subjects are allowed to re-screen for this study one time; this 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 (with the exception of a disqualifying Screening genotype which may not be retested; however, a single repeat test for a failed genotype [no result] is permitted during the Screening period).

Randomised Phase: Day 1 to Week 48 + 4-week treatment extension

Subjects who fulfil eligibility requirements will be randomised 1:1 to receive DTG once daily + two NRTIs or LPV/RTV once or twice daily + two NRTIs. The investigator selected background regimen must be determined and documented prior to randomisation and should take into account Screening genotypic resistance testing results as well as prior treatment history and, if available, any previous genotypic (and phenotypic) results. The background regimen shall be composed of at least one fully active NRTI based on Screening resistance testing plus one more NRTI which may or may not be active (as

defined in Section 5.1.3). For further detail on the definition of full or partial activity, see Section 5.1.3.

When constructing a subject's background NRTI regimen, certain combinations of NRTIs are prohibited (see Section 5.1.3). Following Day 1, no changes or intensification of background regimen will be permitted prior to meeting confirmed virologic withdrawal criteria or Week 52, with the exception of one allowed background NRTI change for management of drug toxicity as described in Section 6.4.4, "Specific Toxicities/Adverse Event Management". Any NRTI change must ensure a fully active NRTI is still present based on Screening resistance testing. A switch from 3TC to FTC (or vice versa) will not be considered a background NRTI change and will not incur a penalty as per the FDA's Snapshot algorithm (Missing, Switch or Discontinuation = Failure) (see Section 6.3.2 and Section 8.3.2).

In order to achieve balance across the two treatment groups of the study, randomisation will be stratified by:

- Screening plasma HIV-1 RNA (≤100,000 c/mL or >100,000 c/mL);
- Number of fully active NRTIs in the investigator selected background regimen based on Screening genotype (as defined in Section 5.1.3): 2 versus <2.

During the Randomised Phase, subjects will attend the clinic at Baseline/Day 1 and at Weeks 4, 8, 16, 24, 36, 48 and 52 of treatment.

Subjects are considered to have completed the Randomised Phase of the study if they remain on therapy (i.e. have not permanently discontinued IP) through completion of the Week 52 visit.

Following the Week 48 visit, subjects will stay on their DTG or LPV/RTV-based regimen for another 4 weeks (i.e. the 4-week treatment extension). Any subject with a viral load of ≥50 c/mL at Week 48 will have their viral load confirmed by a second measurement performed at the Week 52 visit. As per the primary endpoint, if the retest viral load is <50 c/mL then the subject will be considered to have met the primary endpoint of virologic responder by FDA's Snapshot algorithm at Week 48 (see Section 6.3.2). If the retest viral load is ≥50 c/mL then the subject will be considered to be a virologic non-responder at Week 48 by Snapshot analysis. Thus, the treatment extension up to Week 52 will allow for a robust assessment of treatment response in the primary endpoint analysis at Week 48 (windowed) as transient blips in HIV RNA ≥50 c/mL are censored.

All subjects will attend the clinic at Week 52.

Following the IDMC's recommendation and as per Protocol Amendment No. 2, subjects randomised to the LPV/RTV arm will either (i) continue receiving LPV/RTV and complete the study after the 4-week treatment extension at Week 52, or (ii) switch to the DTG arm prior to study completion at Week 52 and continue to have access to DTG in the Continuation Phase.

The primary efficacy endpoint corresponds to viral load measurements collected within a ± 6 week window around the Week 48 visit (including data from the Week 52 visit), as per the FDA's Snapshot algorithm, and for this reason, the primary analysis is denoted as occurring at Week 48 with the understanding that data from the Week 52 visit may be included.

DTG Continuation Phase

Subjects randomised to receive DTG who successfully complete 52 weeks of treatment and subjects originally randomised to receive LPV/RTV but switched to DTG prior to Week 52 (as per Protocol Amendment No. 2) will continue to have access to DTG (Continuation Phase) until it is either locally approved and commercial supplies are available to patients (e.g. through public health services), the patient no longer derives clinical benefit, or the patient meets a protocol-defined reason for discontinuation. Investigative sites must make arrangements for provision of background NRTIs to all subjects to ensure continued access to these medications during the DTG Continuation Phase (unless provision by the sponsor is mandated by local regulation).

Subjects randomised to the LPV/RTV arm will receive LPV/RTV + two NRTIs through their Week 52 visit only, after which subjects will complete the study and will need to have alternate arrangements in place to access antiretroviral medication (unless mandated by local regulation). Subjects randomised to the LPV/RTV arm, who switch to the DTG arm prior to study completion at Week 52, will continue to have access to DTG (Continuation Phase) as mentioned above.

Study Completion

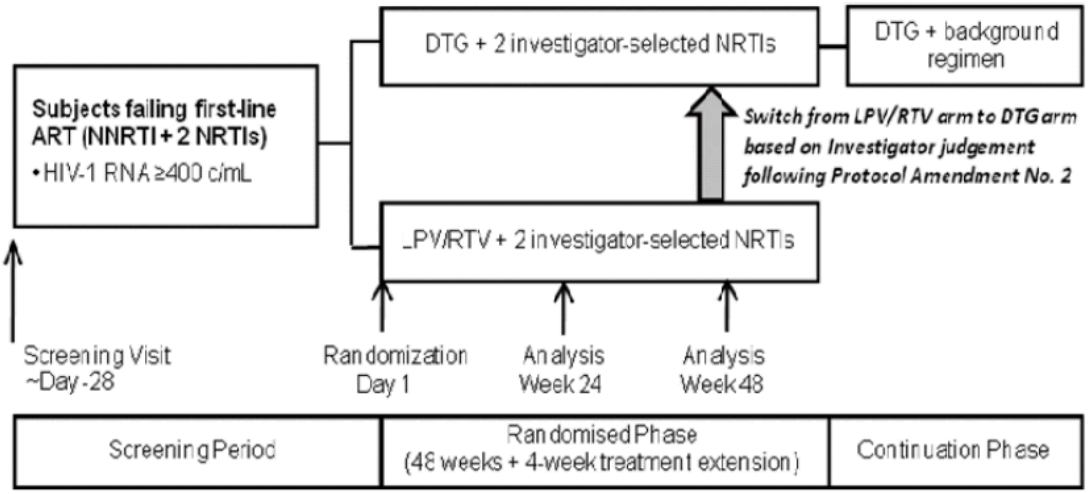
Subjects are considered to have completed the study if they satisfy one of the following:

- Randomised to LPV/RTV + two NRTIs and completed the Randomised Phase including the Week 52 study visit;
- Randomised to LPV/RTV + two NRTIs, switched to DTG + two NRTIs and completed the Randomised Phase including the Week 52 study visit, and did not enter the Continuation Phase;
- Randomised to LPV/RTV+ two NRTIs, switched to DTG + two NRTIs and completed the Randomised Phase, including the Week 52 study visit, entered and completed the Continuation Phase (defined as remaining on study until commercial supplies of DTG become locally available to patients [e.g. through public health services]).
- Randomised to DTG + two NRTIs, completed the Randomised Phase including the Week 52 study visit, and did not enter the Continuation Phase;
- Randomised to DTG + two NRTIs, completed the Randomised Phase, including the Week 52 study visit, entered and completed the Continuation Phase (defined as remaining on study until commercial supplies of DTG become locally available to patients [e.g. through public health services]).

Follow Up

Subjects with ongoing AEs or laboratory abnormalities considered to be AEs will attend a Follow-up visit approximately four weeks after their last dose of IP (DTG or LPV/RTV). 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.

Figure 1 Study Schematic



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 (Section 6.1), are essential and required for study conduct.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SPM). The SPM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

3.2. Discussion of Design

The design of this study (1:1 randomised, open-label, active-controlled, multicentre, parallel group) is well established for confirming the non-inferiority of an investigational agent compared to an active comparator and is generally accepted by regulatory authorities as rigorous proof of antiviral activity.

The primary endpoint, proportion of subjects at Week 48 with plasma HIV-1 RNA below the assay lower limit of detection (LLOD, e.g. <50 c/mL), is a reasonable well-established surrogate endpoint for prognosis of HIV-1 infection and disease progression.

LPV/RTV is one of two PIs currently recommended by WHO for treatment of patients experiencing virologic failure on a first line regimen [WHO, 2013; WHO, 2016] and is widely used (in combination with NRTIs) for second line treatment in low to middle

income countries. Several ongoing studies exploring the role of alternative treatment strategies in this patient group have similarly included LPV/RTV as the comparator [SECOND-LINE Study Group, 2013; Paton, 2013].

Consistent with other Phase IIIb and IV studies for other antiretrovirals, the potential for once or twice daily dosing of LPV/RTV and because of the concerns about pill burden, this study will be open-label. However, no summaries of the study data according to actual randomised treatment groups will be available to sponsor staff prior to the planned Week 24 interim analysis.

An IDMC will be used to provide independent review of the accumulating data to ensure subjects are not being sub-optimally treated in either arm (see Section 8.3.4.2 and Section 9.8).

This study is designed to show the potency and safety of DTG compared to LPV/RTV in patients failing first-line ART and to explore the potential of DTG to be used as an alternative option to boosted PIs in second-line treatment regimens.

4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

4.1. Number of Subjects

Sufficient subjects will be screened in order to ensure a total of approximately 612 subjects will be randomised, approximately 306 to each study arm. Subjects will be enrolled from multiple geographic regions.

	Subjects
Screened	~815
Randomised	~612
Evaluable	~612

All randomised and treated subjects (per the ITT-E definition, see Section 8.3.1) are considered evaluable for the primary efficacy analysis, with subjects who discontinue from the study prior to Week 48 being imputed as non-responders.

4.2. Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB, IB supplements, product labels, and/or local prescribing information.

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

Subjects are allowed to re-screen for this study one time; this 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 (with the exception of a disqualifying Screening genotype which may not be retested; however, a single repeat test for a failed genotype [no result] is permitted during the Screening period). A subject that does not have a fully active NRTI based on a resistance test which is successful during Screening should not re-screen.

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).

Eligible subjects must:

- be able to understand and comply with protocol requirements, instructions, and restrictions,
- be likely to complete the study as planned,
- be considered appropriate candidates for participation in an investigative clinical trial with oral medication (e.g. no active substance abuse, acute major organ disease).

Laboratory results from central laboratory services provided by this trial will be used to assess eligibility.

Subjects eligible for enrolment in the study must meet all of the following criteria:

1. HIV-1 infected subjects ≥18 years of age.

2. A female subject may be eligible to enter and participate in the study if she:

    a. is of non-childbearing potential defined as either post-menopausal (12 months of spontaneous amenorrhea and ≥45 years of age) or physically incapable of becoming pregnant with documented tubal ligation, hysterectomy, or bilateral oophorectomy or,

    b. is of child-bearing potential, with a negative pregnancy test at both Screening and Day 1 and agrees to use one of the following methods of contraception to avoid pregnancy throughout the study and for at least 2 weeks after discontinuation of all study medication:

        - Complete abstinence from intercourse from 2 weeks prior to administration of IP.
        - Approved hormonal contraception for subjects randomised to the DTG arm including:
            - Combined oestrogen and progestogen oral contraceptive [Hatcher, 2011])
            - Contraceptive subdermal implant
            - Injectable progestogen [Hatcher, 2011]
            - Contraceptive vaginal ring [Hatcher, 2011]

  - Percutaneous contraceptive patches [Hatcher, 2011]

- Approved hormonal contraception (as for subjects randomised to the DTG arm; see above) and a barrier method for subjects randomised to the LPV/RTV arm.
- Intrauterine device or intrauterine system.
- 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.
- Any other method with published data showing that the expected failure rate is <1% per year.

Any contraception method must be used consistently and in accordance with the approved product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Note: these contraceptive requirements do not apply to females of childbearing potential with same sex partners only, when this is their preferred and usual lifestyle.

All subjects participating in the study should be counselled on safer sexual practices including the use of effective barrier methods (e.g. male condom/spermicide).

3. HIV-1 infection as documented by HIV-1 RNA ≥400 c/mL at Screening.

4. Subject has been on a first-line treatment regimen consisting of an NNRTI plus two NRTIs for at least 6 months and is currently experiencing virologic failure to this first-line regimen defined as two consecutive (≥7 days apart) HIV-1 RNA results of ≥400 c/mL (which can include Screening HIV-1 RNA results).

   In addition to HIV-1 RNA ≥400 c/mL at Screening, at least one previous HIV-1 RNA result of ≥400 c/mL within the 3 months prior to Screening must be documented. If an additional HIV-1 RNA within 3 months prior to Screening is not available, a second HIV-1 RNA must be performed and have results ≥400 c/mL during the Screening period [after the first result is available and ≥7 days apart] to serve as a confirmatory sample.

5. Subjects must receive at least one fully active agent within the dual-NRTI background regimen for second line treatment. Fully active is defined by the Screening genotypic resistance report of the central laboratory (or a laboratory contracted by the central laboratory) showing no evidence of full or of partial resistance for a given NRTI which will be taken on study.

6. Subject is PI-naïve and INI-naïve, defined as no prior or current exposure to any PI or INI.

7. Subject or the subject's legal representative is willing and able to understand and provide signed and dated written informed consent prior to screening.

4.3. Exclusion Criteria

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

A single repeat test (re-test) per analyte is allowed during the Screening period (with the exception of a disqualifying Screening genotype which may not be retested; however, a single repeat test for a failed genotype [no result] is permitted during the Screening period).

Subjects meeting any of the following criteria must not be enrolled in the study:

Exclusionary medical conditions

1. Women who are breastfeeding.

2. Any evidence of an active Centers for Disease Control and Prevention (CDC) Category C disease (Section 11.2). Exceptions include cutaneous Kaposi's sarcoma not requiring systemic therapy and historic or current CD4+ cell levels <200 cells/mm^3.

3. Subjects with severe hepatic impairment (Class C) as determined by Child-Pugh classification (see Appendix 1, Section 11.1).

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. Anticipated need for hepatitis C virus (HCV) therapy during the Randomised Phase of the study.

6. History or presence of allergy or intolerance to the study drugs or their components or drugs of their class.

7. Ongoing malignancy other than cutaneous Kaposi's sarcoma, basal cell carcinoma, or resected, non-invasive cutaneous squamous cell carcinoma, or cervical intraepithelial neoplasia; other localised malignancies require agreement between the investigator and the Study medical monitor for inclusion of the subject.

8. Subjects who in the investigator's judgment, poses a significant suicidality risk. Recent history of suicidal behaviour and/or suicidal ideation may be considered as evidence of serious suicide risk.

Exclusionary Treatments prior to Screening or Day 1

9. Treatment with an HIV-1 immunotherapeutic vaccine within 90 days of Screening.
10. Treatment with any of the following agents within 28 days of Screening:
    - radiation therapy,
    - cytotoxic chemotherapeutic agents,
    - systemically administered immunomodulators.
11. Treatment with any agent, other than licensed ART as allowed above (Section 4.2), with documented activity against HIV-1 *in vitro*/*vivo* within 28 days of first dose of IP. The exception is use of entecavir, in appropriate clinical situations, for treatment of hepatitis B (e.g. prior intolerance to TDF, viral resistance to 3TC /FTC) after discussion and agreement between the investigator and the medical monitor.
12. 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.

Exclusionary Laboratory Values or Clinical Assessments at Screening

13. Any evidence of primary viral resistance to PIs or INIs based on the presence of any major resistance-associated mutation [Johnson, 2013].
14. The subject's virus does not yield results using genotype at Screening (assay data is essential for eligibility determination).
15. Any verified Grade 4 laboratory abnormality, with the exception of Grade 4 triglycerides. A single repeat test is allowed during the Screening period to verify a result.
16. Any acute laboratory abnormality at Screening, which, in the opinion of the Investigator, would preclude the subject's participation in the study of an investigational compound.
17. Alanine aminotransferase (ALT) ≥5 times the upper limit of normal (ULN) *or* ALT ≥3xULN **and** bilirubin ≥1.5xULN (with >35% direct bilirubin).

Notwithstanding these minimum inclusion and exclusion criteria, Investigators must also follow country specific guidelines where they exist when making decisions about subjects who are eligible for study participation.

4.4. Other Eligibility Criteria Considerations

To assess any potential impact on subject eligibility with regard to safety, the Investigator must refer to the IB and supplements, approved product labels, and/or local prescribing information for detailed information regarding warnings, precautions, contraindications, AEs, drug interactions, and other significant data pertaining to the IP.

4.5. Withdrawal Criteria

Subjects permanently discontinuing study treatments prior to Week 52 are considered to be withdrawn from the study treatments and also from the study. Similarly, subjects in the DTG arm who enter the Continuation Phase but permanently discontinue participation in the Continuation Phase prior to commercial supplies of DTG becoming available to patients (e.g. through public health services), are considered to be withdrawn from study treatment and also from the study.

A subject may voluntarily discontinue participation in this study at any time. The Investigator may also, at their discretion, discontinue the subject from participating in this study at any time. Withdrawn subjects will not be replaced.

Subjects **may** be prematurely discontinued from the study for any of the following reasons:

- Subject or Investigator non-compliance;
- At the request of the subject, Investigator, or Sponsor;
- 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 **must** be discontinued from the study for any of the following reasons:

- Confirmed virologic withdrawal criteria as described in Section 4.6.1 are met;
- Subject requires substitution or dose modification of DTG, or substitution of LPV/RTV (a switch from LPV/RTV 800/200 mg once daily to 400/100 mg twice daily or the opposite switch is allowed; as per Protocol Amendment No. 2, a switch from LPV/RTV to DTG will also be allowed);
- Subject requires a second switch of background therapy prior to Week 52 (one switch in NRTIs is allowed for toxicity management but any NRTI change must ensure a fully active NRTI is still present based on Screening resistance testing, see Section 6.4.4). A switch from 3TC to FTC (or vice versa) will not be considered a background NRTI change and will not incur a penalty as per the Snapshot algorithm (see Section 6.3.2 and Section 8.3.2).
- Liver toxicity where stopping criteria specified in Section 6.4.4.1 are met and no compelling alternate cause is identified;
- Grade 4 clinical AE considered causally related to IP (see Section 6.4.3);
- Renal toxicity criteria as specified in Section 6.4.4.5 are met and no compelling alternate cause is identified;

- Allergic reaction or rash criteria as described in Section 6.4.4.6 and Section 6.4.4.7 respectively, are met and no compelling alternate cause is identified;

- Pregnancy (intrauterine), regardless of termination status of pregnancy (Section 6.4.11). As a reminder, females of childbearing potential who changed their minds and desire to become pregnant, or who state they are no longer 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, perform the procedures described in the Time and Events Table (Section 6.1) for the Withdrawal visit and if necessary the Follow Up visit. 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. A Follow-up visit may occur approximately 4 weeks after the last dose of study treatment and is only required in subjects with ongoing clinical or laboratory AEs at the time of Withdrawal.

Should a subject fail to attend the clinic for a required study visit, the site should attempt to contact the subject and re-schedule the missed visit as soon as possible. The site should also 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 based on previous non-compliance. In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject (e.g. via telephone calls and/or sending a certified letter to the subject's last known mailing address) so that they can appropriately be withdrawn from the study. These contact attempts should be documented in the subject's medical record. Should the subject continue to be unreachable, then he/she will be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up". For all other subjects withdrawing from the study, an alternative reason for discontinuation should be recorded in the electronic case report form (eCRF).

Subjects are not obligated to state the reason for withdrawal. However, the reasons for withdrawal, or failure to provide a reason, must be documented by the Investigator on the Completion/Withdrawal section of the CRF. Every effort should be made by the Investigator to follow up subjects who withdraw from the study. In the event that a subject is prematurely discontinued from the study at any time due to an AE (see Section 6.4.3) the procedures stated in the Time and Events Table (Section 6.1) must be followed. Subjects who are withdrawn from the study will not be replaced.

Subjects may have a temporary interruption to their study treatment for management of toxicities (Section 6.4.3).

4.6. Virologic Criteria for Subject Management and Viral Resistance Testing

For the purposes of clinical management in this study, suspected or confirmed virologic withdrawal criteria are defined in Section 4.6.1 wherein the virologic withdrawal criteria

defined below revolve around the HIV-1 RNA cut-off of 400 c/mL. Notably, this allows for more reliable generation of data required for subject management as the primary genotypic and phenotypic resistance assays are not validated for RNA levels near the limits of detection (50 c/mL).

Following Day 1, no changes, or intensification of ART will be permitted prior to meeting confirmed virologic withdrawal criteria or Week 52, with the exception of a switch from LPV/RTV 800/200 mg once daily to 400/100 mg twice daily or the opposite switch, a switch from LPV/RTV to DTG as per Protocol Amendment No. 2, and one allowed background NRTI change for management of drug toxicity as described in Section 6.4.4., "Specific Toxicities/Adverse Event Management". Any NRTI change must ensure a fully active NRTI is still present based on Screening resistance testing. A switch from 3TC to FTC (or vice versa) will not be considered a background NRTI change and is permitted. Subjects unable to manage drug toxicity or tolerate IP (DTG or LPV/RTV) must be discontinued from the study as described in Section 6.4.

4.6.1. Virologic Withdrawal Criteria

Virologic withdrawal criteria must be confirmed for each criterion by a repeat and consecutive plasma HIV-1 RNA measurement between one and four weeks after the subject met a suspected virologic withdrawal criterion. Subjects should receive full dose of IP across all plasma sampling times used for determining virologic non-response or rebound. For these definitions, Baseline viral load is defined as the Day 1 HIV-1 RNA measurement. For the purposes of clinical management in this study, virologic withdrawal criteria are defined as any of the following:

Virologic Non-response

- A decrease in plasma HIV-1 RNA of less than 1 $\log_{10}$ c/mL by Week 16, with subsequent confirmation, unless plasma HIV-1 RNA is <400 c/mL.
- Confirmed plasma HIV-1 RNA levels ≥400 c/mL on or after Week 24.

Virologic Rebound

- Confirmed rebound in plasma HIV-1 RNA levels to ≥400 c/mL after prior confirmed suppression to <400 c/mL.

Subjects who meet any confirmed virologic withdrawal criterion must be discontinued from the study.

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

4.6.2. Managing Subjects Meeting Suspected Virologic Withdrawal Criteria

Only plasma HIV-1 RNA values determined by the central laboratory (or a laboratory contracted by the central laboratory) will be used to assess virologic withdrawal criteria.

Upon notification that a subject's HIV-1 RNA plasma level qualifies him/her as meeting a suspected virologic withdrawal criterion, the Investigator should query the subject regarding intercurrent illness, recent immunisation, or interruption of therapy as inadequate adherence is a common cause of elevated HIV-1 RNA measurements.

All cases that meet a suspected virologic withdrawal criterion must be confirmed by a second measurement performed at least one week but not more than 4 weeks apart from the date of the original sample, unless one of the extenuating circumstances outlined below applies.

The following guidelines will 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 dose of all IP.
- Confirmatory testing should be scheduled at least 4 weeks following any immunisation, during which time the subject should receive full dose of IP.
- 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 dose of IP.
- The subject should have received full doses of IP for at least 2 weeks at the time confirmatory plasma HIV-1 RNA is done.

Sites should contact GSK to discuss individual subjects, whenever necessary.

At Week 48, repeat HIV-1 RNA testing is required for any HIV-1 RNA between ≥50 c/mL and <400 c/mL and must be performed at the Week 52 study visit (see Section 4.7).

4.6.3. Managing Subjects Meeting Confirmed Virologic Withdrawal Criteria

Once a subject has been confirmed as meeting a virologic withdrawal criterion, a 'plasma for storage' sample from the virologic failure visit and the Day 1 sample will be sent as soon as possible for genotypic and phenotypic resistance testing and the result made known to the Investigator when available.

A subject who meets a confirmed virologic withdrawal criterion must be discontinued from the study.

If a subject is prematurely discontinued from participation in the study, the Investigator must make every effort to perform the evaluations outlined in the Time and Events Schedule (Section 6.1). These data will be recorded, as they comprise an essential evaluation that needs to be done before discharging any subject from the study.

4.7. Retest Criteria for Subjects with Plasma HIV-1 RNA Levels between ≥50 c/mL and <400 c/mL at Week 48

Subjects with plasma HIV-1 RNA levels between ≥50 c/mL and <400 c/mL at Week 48 must have HIV-1 levels re-assessed by a second measurement performed at the Week 52 visit. Subjects should have received full doses of IP for at least 2 weeks at the time of HIV-1 RNA re-assessment for any HIV-1 RNA level ≥50 c/mL.

Subjects with plasma HIV-1 RNA levels ≥400 c/mL should have a second measurement performed as outlined in Section 4.6.2 "Managing Subjects Meeting Suspected Virologic Withdrawal Criteria".

4.8. Screening Failures

A subject is considered a screening failure if after providing informed consent, the subject's circumstances or conditions change or the outcome of a test or assessment becomes available which results in the subject's failure to meet one or more of the entry criteria, or results in the investigator deciding that the subject is no longer an appropriate study candidate.

Subjects are allowed to re-screen for this study one time (so long as the first screening does not exclude the subject based on lack of a fully active drug); re-screening will require a new subject number. There is no timeline restriction for re-screening.

A single repeat test (re-test) per analyte or assessment is allowed during the screening period to determine eligibility (with the exception of a disqualifying Screening genotype which may not be retested; however, a single repeat test for a failed genotype [no result] is permitted during the Screening period to determine eligibility).

Laboratory results from central laboratory services provided by this trial will be used to assess eligibility.

5. STUDY TREATMENTS

5.1. Investigational Product and Other Study Treatment

Investigational product (IP) in this protocol refers to the investigational study drug DTG and the comparator drug LPV/RTV. These will be supplied by GlaxoSmithKline. For this protocol, other antiretrovirals administered in the study are not considered IP.

Investigators will choose a dual NRTI background regimen for each subject (see Section 5.1.3). Background antiretroviral therapy will be recorded on the Concomitant Antiretroviral Therapy (ConART) eCRF page. For additional details, please consult the SPM.

Under normal conditions of handling and administration, IP is not expected to pose significant safety risks to site staff. A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from GSK upon request.

IP must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of the IP will be limited to the investigator and authorised site staff. IP must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

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

5.1.1. Tablet Formulation of DTG

DTG tablets are packaged into high density polyethylene (HDPE) bottles with child-resistant closures that include induction seals. The bottles may contain a desiccant. The recommended storage conditions and expiry date where required, are stated on the product label.

In general, subjects should keep IP in the original container. However, subjects may use pill boxes for short term storage of ≤7 days.

5.1.2. Tablet Formulation of LPV/RTV

LPV/RTV [Kaletra Package Insert, 2016; Kaletra EU Summary of Product Characteristics, 2017] is supplied as the LPV/RTV oral tablet, which contains 200 mg of LPV and 50 mg of RTV. LPV/RTV tablets are manufactured by Abbvie. Each HDPE bottle is closed with a propylene cap and contains 120 tablets.

5.1.3. Background NRTIs

The investigator selected dual NRTI background regimen must be determined and documented prior to randomisation. While Screening resistance test results must be used to determine one fully active agent, all available data (prior treatment history, Screening and historical resistance results) should be considered for selection of the background therapy. The background regimen shall be composed of one of the following:

- one fully active NRTI plus one inactive or partially active NRTI;
- two fully active NRTIs;
- one of the above plus, where required in subjects co-infected with HBV, 3TC.

Note: In consultation with the medical monitor, 3TC may be added as a third NRTI to a dual-NRTI background regimen in subjects with chronic HBV infection and evidence of HIV resistance to 3TC (e.g. M184V) (see Section 6.2.3). 3TC cannot be added to regimens that include FTC.

Fully active is defined by the genotypic resistance report of the central laboratory (or a laboratory contracted by the central laboratory) showing no evidence of full or of partial resistance for a given NRTI. For additional details, please consult the SPM.

All triple NRTI (except for adding 3TC to a dual NRTI combination in subjects co-infected with HBV; see Section 6.2.3) and the following dual NRTI combinations will be

prohibited in this protocol per current treatment guidelines and recommendations [HHS 2013; Gallant, 2005; Barnas, 2010]:

- ABC+TDF,
- 3TC+FTC,
- AZT+d4T,
- ddI+ABC,
- ddI+TDF,
- ddI+d4T,
- ddI+3TC,
- ddI+FTC,
- d4T+3TC,
- d4T+FTC.

All background NRTIs are locally registered products. GSK will not reimburse or supply the investigator selected background regimen unless requested by the local regulatory authority or IRB/IEC or unless previously agreed with study sites.

Those subjects for whom ABC is being considered as a component of the NRTI backbone should have been screened and be negative for the HLA-B*5701 allele before randomisation takes place (see Section 6.2.1). This testing may be conducted as part of the study or may be performed by local laboratories. Results must be available for source document verification.

5.1.4. Dosage and Administration

Details of dosing for both randomised arms are outlined in the following table:

Treatment Arm	IP Dose and Dose Interval and background NRTI
DTG	1 x 50 mg DTG tablet once daily plus 2 NRTIs selected by the investigator
LPV/RTV	4 x 200/50 mg LPV/RTV tablets once daily **or** 2 x 200/50 mg LPV/RTV tablets twice daily plus 2 NRTIs selected by the investigator

IP may be administered with or without food.

5.1.5. Protocol-Permitted Substitutions

A switch of DTG or LPV/RTV is not allowed except for a switch from LPV/RTV 800/200 mg once daily to LPV/RTV 400/100 mg twice daily or the opposite switch. As per Protocol Amendment No. 2, a switch from LPV/RTV to DTG will be allowed.

Switch of one background NRTI to an alternative approved NRTI for toxicity or tolerability management is allowed one time. After the switch, based on Screening resistance testing results background ART must still consist of at least one fully active

NRTI and a second single NRTI which may or may not be active (as defined in Section 5.1.3). A switch from 3TC to FTC (or vice versa) will not be considered a background NRTI change and is permitted. The date of the decision to switch one background NRTI for toxicity or tolerability management must be documented in the eCRF.

Local prescribing information should be consulted for information regarding use of these medications.

For more details on IP and protocol-permitted switch medications, refer to the SPM.

5.2. Treatment Assignment

Informed consent must be obtained prior to any study procedures, including any Screening assessment.

Subjects will be assigned to study treatment in accordance with the randomisation schedule. Randomisation will occur at the Baseline (Day 1) visit and will be conducted via a central randomisation procedure following confirmation of fulfilment of study entry criteria. Subjects will be assigned (1:1) to study treatment in accordance with the computer generated randomisation schedule. The central randomisation schedule, including stratification, will be generated using the GSK validated randomisation software RandAll NG. Study site personnel will be required to contact the central randomisation service for assignment of a unique identifier (designating the subject's randomisation code) for each subject participating in the study. A unique treatment number will be assigned for each subject participating in the study. Subjects will maintain the assigned treatment group throughout the Randomised Phase (Day 1 to Week 48 plus a 4-week treatment extension) and if applicable the Continuation Phase (after Week 52 for subjects randomised to the DTG arm).

Subjects who are randomised into the trial and subsequently withdrawn may not be re-screened.

5.3. Blinding

As this is an open-label study, blinding is not required. No summaries of the study data according to actual randomised treatment groups will be available to sponsor staff prior to the planned Week 24 interim analysis. According to the IDMC Charter, ViiV Healthcare/GSK personnel having direct responsibility for the conduct of the study and its analysis may however review summaries of data by treatment group if the IDMC recommends to the sponsor the termination of a treatment arm or the entire study.

5.4. Product Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of investigational product dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to GSK, when applicable. Product accountability records must be maintained throughout the course of the study.

5.5. Treatment Compliance

Treatment compliance will be evaluated through the Morisky 8-Item Medication Adherence Scale (MMAS-8), a self-report measure of medication-taking behaviour (see Section 6.5). Pill counts of unused IP will be assessed for monitoring purposes each time the subject receives a new (refill) supply of study medication through the Withdrawal visit or study completion. These data will be recorded in the subject's CRF, but will not be summarised for analysis purposes.

5.6. 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 for interactions between such treatments and the study medications. All concomitant medications taken during the study will be recorded in the CRF. The minimum requirement is that the drug name and the dates of administration are to be recorded.

5.6.1. Permitted Medications and Non-Drug Therapies

Concomitant medications (prescription and non-prescription) should be administered only as medically necessary during the study (except prohibited medications described in Section 5.6.2). 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 CRF with dates of administration.

Because non-HIV vaccines may cause a temporary increase in the level of HIV-1 plasma RNA, it is recommended that a vaccine, if necessary, be given during or immediately after a scheduled visit **after** all laboratory tests have been drawn. This approach will minimise the risk of non-specific increases in the level of HIV-1 plasma RNA at the next scheduled assessment.

Entecavir and telbivudine are permitted, in appropriate clinical situations, for treatment of hepatitis B (e.g. prior intolerance or viral resistance to TDF, viral resistance to 3TC/FTC) after discussion and agreement between the investigator and the medical monitor (also see Section 6.2.3).

Approved hormonal contraception may be administered with DTG. However, the investigator should consult local prescribing information for guidance on the use of hormonal contraceptives with background ART as some antiretrovirals have clinically significant drug interactions with these products.

DTG should be administered 2 hours before or 6 hours after taking antacid products or sucralfate containing divalent cations (e.g. aluminum and magnesium). Proton pump inhibitors and H2-antagonists may be used in place of antacids with no scheduling restrictions. Concurrent administration with multivitamins is acceptable.

DTG can be co-administered with calcium or iron supplements if taken with a meal. Under fasted conditions, DTG should be given 2 hours prior to OR 6 hours after calcium or iron supplements.

Metformin concentrations may be increased by DTG. Subjects should be monitored during therapy and a dose adjustment of metformin may be considered.

Both LPV and RTV are inhibitors of the P450 isoform CYP3A. LPV/RTV is likely to increase plasma concentrations of medicinal products that are primarily metabolised by CYP3A. These increases of plasma concentrations of co-administered medicinal products could increase or prolong their therapeutic effect and adverse events. It is important to consult the current prescribing information for LPV/RTV prior to administering any concomitant medication together with LPV/RTV.

5.6.2. Prohibited Medications and Non-Drug Therapies

HIV immunotherapeutic vaccines are not permitted at any time during the study (see Section 5.6.1 for guidance regarding non-HIV vaccines). Other experimental agents, antiretroviral drugs not otherwise specified in the protocol, cytotoxic chemotherapy, or radiation therapy may not be administered (see Exclusion Criteria, Section 4.3).

Systemically administered immunomodulators are prohibited with the following exception. HCV therapy will not be permitted during the Randomised Phase (Day 1 to Week 48 plus a 4-week treatment extension) of the study. If HCV therapy is required during the Continuation Phase, subjects may be allowed to continue on study after discussion and agreement between the investigator and the medical monitor.

Chronic use of systemic (oral or parenteral) glucocorticoids must be avoided; however, short treatment courses (for example, 30 days or less), replacement therapy (e.g. for Addison's Disease), and topical, inhaled, or intranasal use of glucocorticosteroids will be allowed.

Acetaminophen is not to be used in patients with acute viral hepatitis.

For a detailed list of prohibited medications, please consult the SPM.

5.6.3. Prohibited medications for subjects randomised to DTG

The following medications or their equivalents may cause decreased concentrations of DTG. Therefore, the following medications must not be administered concurrently with DTG.

- Carbamazepine
- Oxcarbamazepine
- Phenobarbital
- Phenytoin
- Rifampicin or rifapentine (see Section 5.7 for substitutes for treatment of TB)

- St. John's wort (*Hypericum perforatum*)

Dofetilide and pilsicainide are prohibited as DTG may inhibit their renal tubular secretion resulting in increased dofetilide/pilsicainide concentrations and potential for toxicity.

For NRTIs used as background therapy, please refer to the local prescribing information for information on concurrent therapies.

5.6.4. Prohibited medications for subjects randomised to LPV/RTV

Both LPV and RTV are inhibitors of the P450 isoform CYP3A. LPV/RTV should not be co-administered with medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life threatening events. For subjects randomised to LPV/RTV, the following medications or their equivalents must not be administered concurrently:

- Alfuzosin
- Amiodarone
- Antihistamines (astemizole, terfenadine)
- Cisapride
- Ergot alkaloids (dihydroergotamine, ergonovine, ergotamine, methylergonovine)
- Fusidic acid (in dermatological infections)
- HMG Co-A reductase inhibitors (specifically lovastatin, simvastatin)
- Pimozide
- Rifampicin (see Section 5.7 for substitutes for treatment of TB)
- Sildenafil (when used for the treatment of pulmonary arterial hypertension)
- Vardenafil
- Avanafil
- Midazolam (oral)
- Triazolam
- St John's wort (*Hypericum perforatum*)

Refer to the most up to date prescribing information for LPV/RTV for a listing of drugs with established or other potentially significant interactions with LPV/RTV.

For NRTIs used as background therapy, please refer to the local prescribing information for information on concurrent therapies.

5.7. Treatment of Tuberculosis

Patients who developed tuberculosis (TB) during the study may be managed according to local treatment guidelines with rifabutin substituted for rifampicin. Rifabutin may be reimbursed by GSK.

Switching to DTG twice daily dosing in subjects who receive DTG in this study and require rifampicin treatment for tuberculosis, will not be allowed in this study.

5.8. 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 patient's medical condition whether or not GSK is providing specific post study treatment.

Subjects randomised to DTG

To provide continued access to unapproved investigational drug to subjects deriving therapeutic benefit, subjects randomised to receive DTG and who have successfully completed the Randomised Phase (Day 1 to Week 48 plus a 4-week treatment extension) will be given the opportunity to continue to receive DTG until one of the following occurs:

- DTG is locally approved and commercial supplies are available to patients (e.g. through public health services),
- The subject no longer derives clinical benefit from treatment with DTG, or
- The subject meets a protocol-defined reason for discontinuation.

Investigative sites must make arrangements for provision of background NRTIs to all subjects to ensure access to these medications during and post study.

Subjects who complete the DTG Continuation Phase must return to clinic when transitioning to ART available, e.g. through public health services, to have the assessments performed as noted in the Continuation Phase schedule (see Section 6.1).

Subjects randomised to LPV/RTV

As subjects receiving LPV/RTV in the Randomised Phase (Day 1 to Week 48 plus a 4-week treatment extension) complete the Week 52 visit, they will also complete the study. Investigative sites must make arrangements for provision of LPV/RTV early during the study to ensure continued access to medication post study. Investigative sites must make arrangements for provision of background NRTIs to all subjects to ensure access to these medications during and post study.

Subjects originally randomised to receive LPV/RTV but switched to the DTG arm prior to Week 52 (as per Protocol Amendment No. 2) will continue to have access to DTG (Continuation Phase) until it is either locally approved and commercial supplies are

available to patients (e.g. through public health services), the patient no longer derives clinical benefit, or the patient meets a protocol-defined reason for discontinuation. Investigative sites must make arrangements for provision of background NRTIs to all subjects to ensure continued access to these medications during the DTG Continuation Phase (unless provision by the sponsor is mandated by local regulation).

5.9. Treatment of Study Treatment Overdose

Any tablet intake exceeding the randomised daily number of tablets for IP will be considered an overdose.

For the purposes of this study, an overdose is not an AE (see Section 6.4.5.1) 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 6.4.5.2).

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

The Investigator should use clinical judgment and also refer to the prescribing information for approved ARTs, as appropriate in treating overdose, as GSK is unable to recommend specific treatment.

6. STUDY ASSESSMENTS AND PROCEDURES

6.1. Time and Events Schedule

Table 1 Time and Events Table

Procedures			Randomised Phase							Continuation Phase[b]		Withdrawal	Follow-up[c]
	Screening[a]	Baseline (Day 1)	Day 1 to Week 48						4-week Treatment Extension				
			Week 4	Week 8	Week 16	Week 24	Week 36	Week 48	Week 52	Week 60	Every 12 weeks thereafter		
Clinical and Other Assessments													
Written informed consent	X												
Inclusion/Exclusion criteria[d]	X												
Subject demography	X												
Medical history[e]	X												
Prior ART history	X												
CDC HIV-1 classification	X	X											
Limited physical examination[f]	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight and height		X											
Current medical conditions		X											
CV risk assessment[g]		X											
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X

Procedures			**Randomised Phase**							**Continuation Phase[b]**		**Withdrawal**	**Follow-up[c]**
	Screening[a]	**Baseline (Day 1)**	**Day 1 to Week 48**						**4-week Treatment Extension**				
			Week 4	**Week 8**	**Week 16**	**Week 24**	**Week 36**	**Week 48**	**Week 52**	**Week 60**	**Every 12 weeks thereafter**		
HIV associated conditions			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	
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X
SAEs	X[i]	X	X	X	X	X	X	X	X	X	X	X	X
GSRS		X	X			X		X				X[j]	
HIVTSQs		X	X			X		X				X[j]	
HIVTSQc								X				X[j]	
MMAS-8		X	X			X		X				X[j]	
Laboratory Assessments													
Quantitative plasma HIV-1 RNA PCR	X	X	X	X	X	X	X	X	X[k]	X	X	X	
Lymphocyte subset	X	X	X	X	X	X	X	X	X	X	X	X	
Plasma for HIV genotyping	X												
Plasma for storage[l]	X	X	X	X	X	X	X	X	X	X	X	X	
HLA-B* 5701 testing[m]	X												
Clinical chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X
Haematology	X	X	X	X	X	X	X	X	X	X	X	X	X
PT/INR	X												
Fasting lipids and glucose[n]		X			X	X		X					
Pregnancy test[o]	S	U	S	S	S	S	S	S	S	S	S	S	S
HBsAg, anti-HBc and anti-HCV[p]	X												

Procedures			**Randomised Phase**							**Continuation Phase[b]**		**Withdrawal**	**Follow-up[c]**
	Screening[a]	**Baseline (Day 1)**	**Day 1 to Week 48**						**4-week Treatment Extension**				
			Week 4	**Week 8**	**Week 16**	**Week 24**	**Week 36**	**Week 48**	**Week 52**	**Week 60**	**Every 12 weeks thereafter**		
HBV DNA[q]		X											
Pharmacogenetic sample[r]		X											
PBMCs[s]		X											
Investigational product													
Interactive voice recognition system (IVRS)	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense IP		X	X	X	X	X	X	X	X[t]	X	X		
IP accountability (pill counts)			X	X	X	X	X	X	X	X	X	X	

a. The 28-day Screening period may be extended to 42 days. Randomisation may occur as soon as all Screening results are available.
b. For subjects who completed randomised DTG through Week 52 and entered into the DTG Continuation Phase: subjects completing the DTG Continuation Phase must return to the clinic when transitioning to commercial supplies. Conduct study assessments, with the exception of dispensing IP, as specified for all Continuation Phase visits at this end of Continuation Phase visit.
c. A follow-up visit will be conducted 4 weeks after the last dose of study provided IP and is required only if a subject has ongoing AEs or laboratory abnormalities at the last on-study visit. The assessments performed should reflect what is considered medically necessary to assess the event(s).
d. Inclusion/exclusion criteria will be fully assessed at the Screening visit. Changes between the screening visit and the Day 1 visit should be assessed to ensure eligibility, including additional assessments performed at Day 1.
e. Full medical history will be collected. Targeted Medical History assessments will include cardiovascular, gastrointestinal (e.g. GI bleeding, PUD, etc), metabolic (e.g. Type I or II DM), psychiatric (e.g. depression), renal (e.g. nephrolithiasis, nephropathy, renal failure) and neurological disorders.
f. Limited physical examination to include blood pressure at Baseline (recorded in eCRF) for Framingham score assessment. Blood pressure to be measured after resting in a semi-supine position for at least 5 minutes.
g. Assessment for cardiovascular risk will include height, weight, blood pressure, smoking history, medical conditions, and family history of premature cardiovascular disease.
h. On Day 1, the Columbia Suicidality Severity Rating Scale is to be administered prior to randomisation.
i. Only SAEs related to study participation or to a concomitantly administered GSK/ViiV product will be collected between obtaining informed consent and administration of IP at Day 1.
j. Health outcomes assessments will only be conducted at Withdrawal if the Withdrawal visit occurs at or prior to Week 48.

k. At Week 52, repeat HIV-1 RNA testing will only be performed for subjects with HIV-1 RNA ≥50 c/mL at Week 48.
l. Plasma samples for storage will be collected at each visit for possible future analyses (including but not limited to HIV-1 RNA genotypic and phenotypic analyses, HIV-1 RNA levels, and immunological parameters). These samples will be used when needed such as when samples are lost or arrive at the laboratory unevaluable. Additionally, for genotypic and phenotypic resistance analyses Baseline samples from all subjects will be used and later samples in cases of confirmed virologic withdrawal criteria met (for paired baseline and endpoint genotypes).
m. Subjects starting ABC as one of the NRTIs should have been screened and be negative for the HLA-B*5701 allele.
n. An overnight fast is preferred, however a minimum of a 6 hour fast is acceptable.
o. Pregnancy testing will be conducted (women of child bearing potential only) on serum (S) samples with the exception of Day 1, which must be a urine (U) test to confirm status prior to administration of IP. Remind females of childbearing potential of the need to avoid pregnancy while on study and adherence to the study's contraception requirements.
p. Subjects who are hepatitis B surface antigen (HBsAg) positive require appropriate HBV therapy based on local guidelines (see Section 6.2.3 for details).
q. HBV DNA testing will be performed on Day 1 for subjects with negative HBsAg and positive hepatitis B core antibody (anti-HBc) results at Screening. Subjects with positive anti-HBc and positive HBV DNA results require appropriate HBV therapy based on local guidelines (see Section 6.2.3 for details).
r. Informed consent for optional pharmacogenetics (PGx) research must be obtained before collecting a sample. Collection of the PGx sample at Day 1 is preferred; however, this sample may be collected at any time during the study.
s. Whole blood collection (please refer to the SPM).
t. For subjects receiving DTG during the Continuation Phase only.

6.2. Critical Screening and Baseline Assessments

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

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

6.2.1. Screening Assessments

Assessments to be conducted at Screening are provided in the Time and Events Table (Section 6.1).

Eligible subjects may be randomised as soon as all Screening assessments are complete and the results are available and documented. All subjects will complete a 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 may be extended to 42 days to accommodate availability of all Screening assessment results and scheduling. All Screening results must be available prior to randomisation.

All subjects must provide a plasma sample for determination of viral genotypic resistance at the central laboratory (or a laboratory contracted by the central laboratory). For eligibility the resistance report must show no evidence of either full or of partial resistance for at least one NRTI which will be taken by the subject during study.

Severe hepatic impairment is exclusionary and will be assessed by Child-Pugh grading at Screening (see Appendix 1, Section 11.1).

Hepatitis B surface antigen (HBsAg) will be obtained at Screening to ensure that subjects with chronic active hepatitis B receive appropriate hepatitis B treatment in conjunction with appropriate HIV background regimens for the study. For subjects with positive hepatitis B core antibody (anti-HBc) and negative HBsAg at Screening, HBV DNA testing will be performed on Day 1.

Subjects who meet all entry criteria are randomised and assigned a randomisation number. Subjects not meeting all inclusion and exclusion criteria at initial screen may be re-screened and receive a new subject number one time. Subjects, who are randomised into the trial and subsequently withdrawn from the study for any reason, may not be re-screened.

Investigators must ensure subjects are prepared for randomisation on Day 1, including confirming arrangements for provision of the dual NRTI background regimen and ensuring that these medications will be available for use at the time of the Day 1 visit. Screening resistance test results must be used to determine one fully active agent, but all available data (prior treatment history, Screening and, if available, historical resistance results) should also be considered for selection of the background therapy. Also see Section 5.1.3 for dual NRTI combinations prohibited in this trial.

Selection of the background regimen must be complete prior to randomisation; therefore, after successfully completing all screening procedures, the investigator will determine the most appropriate background regimen for use in the study.

Note: Where HLA-B*5701 screening is considered standard of care, it is recommended that Investigators screen for presence of the HLA-B*5701 allele in any subject for whom an abacavir (ABC)-containing product (e.g. ZIAGEN™, EPZICOM, KIVEXA) may be considered as part of background regimen and HLA-B*5701 status is unknown (even if the subject has previously tolerated ABC). Use of ABC in subjects known to carry HLA-B*5701 is not recommended and should be considered only under exceptional circumstances where potential benefit outweighs the risk and only under close medical supervision.

6.2.2. Baseline (Day 1) Assessments

Assessments to be conducted at Baseline (Day1) are provided in the Time and Events Table (Section 6.1).

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

Cardiovascular medical history/risk factors will be assessed at Baseline, to include smoking status and history and family history of cardiac events.

6.2.3. Subjects Co-infected with Hepatitis B Virus (HBV)

Investigators should consult current treatment guidelines (e.g. [Thompson, 2012]) when considering choice of NRTIs for subjects with chronic HBV infection (HBsAg positive OR anti-HBc positive with HBV DNA present).

In addition, clinical trial and marketed use of 3TC, FTC and TDF have shown that some subjects with chronic HBV disease may experience clinical or laboratory evidence of recurrent hepatitis upon discontinuation of 3TC, FTC or TDF, which may have more severe consequences in subjects with decompensated liver disease. Subjects with HBV co-infection should be advised against self-discontinuation of any medications with anti-HBV activity. If 3TC, FTC or TDF is discontinued in subjects co-infected with HBV, periodic monitoring of both liver chemistry tests and markers of HBV replication should be performed.

Entecavir and telbivudine are permitted, in appropriate clinical situations, for treatment of hepatitis B (e.g. prior intolerance or viral resistance to TDF, viral resistance to 3TC/FTC) after discussion and agreement between the investigator and the medical monitor.

In consultation with the medical monitor, 3TC may be added as a third NRTI to a dual-NRTI background regimen in subjects with chronic HBV infection and evidence of HIV resistance to 3TC (e.g. M184V). 3TC cannot be added to regimens that include FTC.

6.2.4. Subjects Co-infected with Hepatitis C Virus (HCV)

Investigators should consult current treatment guidelines when considering choice of therapy for subjects with chronic HCV infection. Subjects with an anticipated need for HCV therapy during the Randomised Phase (Day 1 to Week 48 plus a 4-week treatment extension) may not be enrolled into this study.

6.3. Efficacy

6.3.1. Efficacy Evaluations

Plasma HIV-1 RNA

Plasma for quantitative HIV-1 RNA will be collected according to the Time and Events Table (Section 6.1). Methods to be used may include but are not limited to the Abbott RealTime HIV 1 Assay lower limit of detection (LLOD) 40 c/mL. In some cases (e.g. where the HIV-1 RNA is below the lower limit of detection for a given assay) additional exploratory methods may be used to further characterise HIV-1 RNA levels.

Lymphocyte Subsets

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 6.1).

HIV-associated Conditions

HIV-associated conditions will be recorded as per the Time and Events Table (Section 6.1) and assessed according to the 1993 CDC Revised Classification System for HIV Infection in Adults (Appendix 2, Section 11.2). Indicators of clinical disease progression are defined as:

CDC Category A at enrolment → Category C event;

CDC Category B at enrolment → Category C event;

CDC Category C at enrolment → New Category C Event;

CDC Category A, B or C at enrolment → Death.

6.3.2. Primary Endpoint

The primary endpoint for this study will be the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm (Missing, Switch or Discontinuation = Failure) for the ITT-E population (see Section 8.3.3.1).

6.3.3. Secondary Efficacy Endpoints

- Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 24 using the Snapshot algorithm;
- Proportion of subjects with plasma HIV-1 RNA <400 c/mL at Weeks 24 and 48 using the Snapshot algorithm;
- Proportion of subjects without virologic or tolerability failure by Weeks 24 and 48, where failure equals treatment-related discontinuation (meeting confirmed virologic withdrawal criteria, treatment-related adverse event, safety stopping criteria, and lack of efficacy;
- Time to viral suppression (HIV-1 RNA <50 c/mL);
- Absolute values and changes from Baseline in CD4+ cell counts at Weeks 24 and 48;
- Incidence of disease progression (HIV-associated conditions, AIDS and death).

6.4. Safety

6.4.1. Safety Evaluations

Safety assessments will include the following:

- Monitoring and recording all AEs and SAEs. Additional information on the Time Period and Frequency of Detecting AEs and SAEs is provided in Section 6.4.12;
- Regular monitoring of haematology, blood chemistry and fasting lipids (parameters to be tested listed in Table 2 below);
- 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);
- Evaluation and documentation of all concomitant medications and blood products;
- Suicidality monitoring using the Columbia Suicide-Severity Rating Scale (Section 6.4.10).

Any appropriately qualified site personnel (e.g. Investigator, sub-Investigator or study coordinator/nurse) can perform assessments. A central laboratory chosen by GSK (or a laboratory contracted by this central laboratory) will undertake all routine scheduled laboratory evaluations within the study. Refer to the Laboratory Manual for specific instructions on sample collection, processing, storage and shipping for each laboratory test.

Table 2 Laboratory Assessments

Haematology	
Platelet Count	Automated WBC Differential:
RBC Count	Neutrophils
WBC Count (absolute)	Lymphocytes
Haemoglobin	Monocytes
Haematocrit	Eosinophils
MCV	Basophils

MCV = mean corpuscular volume, RBC = red blood cells, WBC = white blood cells

Clinical Chemistry			
BUN	Potassium	AST	Total bilirubin[a]
Creatinine[b]	Chloride	ALT	Albumin
Glucose	Total CO_2	Alkaline phosphatase	Creatine phosphokinase
Sodium	Lipase	Phosphate	

BUN = blood urea nitrogen

a. Direct bilirubin will be reflexively performed for all total bilirubin values > 1.5X ULN.
b. Glomerular Filtration Rate (GFR) will be estimated by the central laboratory using the CKD-EPI method [Levey, 2009].

Fasting Lipid Panel[a]
Total cholesterol
HDL cholesterol
LDL cholesterol
Triglycerides

a. For fasting lipids assessments, an overnight fast is preferred; however, a minimum of a 6 hour fast is acceptable.

Other tests
Plasma HIV-1 RNA
CD4+ cell counts
Hepatitis B (HBsAg, anti-HBc) and Hepatitis C (anti-HCV)[a]
Hepatitis B (HBV DNA)[b]
Pregnancy test for women of child bearing potential[c]
HLA-B*5701 screening[d]

a. Screening visit only.
b. Baseline visit only (subjects with negative HBsAg and positive anti-HBc results at Screening only).
c. Urine pregnancy test on Day 1; serum pregnancy test at Screening and Weeks 4, 8, 16, 24, 36, 48, and 52 (and at Week 60 and at 12 weeks intervals thereafter if applicable).
d. HLA-B*5701 screening will be only performed to examine candidates for ABC at discretion of the investigator.

6.4.2. Safety Endpoints

- Incidence and severity of AEs and laboratory abnormalities;
- Absolute values and changes over time in laboratory parameters;
- Change from Baseline in fasting LDL cholesterol at Weeks 24 and 48;
- Change from Baseline in fasting TC/HDL ratio at Weeks 24 and 48;

- The incidence of maximum post-Baseline emergent Grade 2 or greater laboratory abnormalities in fasting LDL cholesterol by Weeks 24 and 48;
- The incidence of maximum post-Baseline emergent Grade 2 or greater drug-related diarrhoea by Weeks 24 and 48;
- The proportion of subjects who discontinue treatment due to AEs.

6.4.3. Toxicity Management

Adverse events that occur during the trial should be evaluated by the Investigator and graded according to the Division of AIDS (DAIDS) toxicity scales (Appendix 3, Section 11.3). Additional information regarding detecting, documenting and reporting AEs and SAEs are available in Section 6.4.5.

IP may be interrupted at the discretion of the Investigator and according to the severity of the AE. If one or more antiretroviral medication is held due to toxicity or adverse events, all antiretroviral medications should be held to reduce the risk of development of resistance taking into account both the length of the planned interruptions and the pharmacokinetic half-life of each antiretroviral of the regimen, in a way to minimise the risk of development of resistance.

No toxicity-related dose reductions of IP will be allowed (except for switch from LPV/RTV 800/200 mg once daily to LPV/RTV 400/100 mg twice daily or the opposite switch). IP 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 IP or temporary interruption of one or more 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 general subject management and IP interruptions based on the severity of the AE; for specific toxicities, please refer to Section 6.4.4 "Specific Toxicities/Adverse Event Management". All changes in the IP must be accurately recorded in the subject's eCRF.

Note: for subjects receiving an ABC-containing product as part of the background regimen, in the event of a discontinuation of ABC for any reason, reinitiation of this drug should be undertaken with caution. The investigator should obtain a complete history of the events surrounding the discontinuation of the ABC-containing product, evaluate for the possibility of a clinically suspected HSR, and initiate subject management as outlined in the Local Country Prescribing Information, regardless of a subject's HLA-B*5701 status. Screening for the presence of HLA-B*5701 is recommended prior to reinitiating treatment with ABC-containing products in subjects of unknown HLA-B*5701 status who have previously tolerated ABC.

Grade 1 or Grade 2 Toxicity/Adverse Event

Subjects who develop a Grade 1 or Grade 2 AE or toxicity may continue IP at the discretion of the Investigator. (**Note**: see Section 6.4.4 "Specific Toxicities/Adverse Event Management" for exceptions to this guideline). Subjects who choose to withdraw

from 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 IP, dosing may continue after discussion with the medical monitor.

Subjects who develop a Grade 3 AE or toxicity, which the Investigator considers related or possibly related to the IP, should have the IP withheld and be rechecked each week until the AE returns to Grade 2. Once the AE is Grade ≤2, IP may be re-started.

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

Subjects with Grade 3 asymptomatic laboratory abnormalities should be investigated for all potential non-drug related causes, and, following discussion with the medical monitor, may continue IP if the Investigator has compelling evidence that the toxicity is not related to IP. Exceptions are noted below for lipid abnormalities (Section 6.4.4.3).

Grade 4 Toxicity/Adverse Event

Subjects who develop a Grade 4 AE or toxicity should have IP permanently discontinued. However, if the Investigator has compelling evidence that the AE is not causally related to the IP, 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 IP 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 Grade 4 asymptomatic 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 IP. Exceptions are noted below for lipid abnormalities (Section 6.4.4.3). A follow-up visit should be performed 4 weeks after the last dose of study medication if AEs or laboratory abnormalities are ongoing.

6.4.4. Specific Toxicities/Adverse Event Management

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

A switch from LPV/RTV 800/200 mg once daily to LPV/RTV 400/100 mg twice daily or the opposite switch is allowed.

Toxicities that the Investigator considers related or possibly related to one of the background NRTIs may be addressed by substitutions of the medication for another approved NRTI one time during the study, as indicated in Section 5.1.5 "Protocol-Permitted Substitutions". Additional background substitutions for toxicity management are permitted after Week 52, but must be agreed first with the study medical monitor.

Toxicities that the Investigator considers related or possibly related to any background NRTI should be managed with reference to applicable product labelling.

Subjects who permanently discontinue IP for reasons of toxicity should be followed weekly until resolution of the AE and encouraged to complete the withdrawal and Follow-Up study evaluations as noted above.

6.4.4.1. 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 IP and the follow-up period. IP will be stopped if any of the following liver chemistry criteria are met:

- ALT ≥ 3xULN and bilirubin ≥2xULN (>35% direct bilirubin; bilirubin fractionation required);

  Note: serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥ 2xULN, then the event meets liver stopping criteria;
- ALT ≥8xULN;
- ALT ≥3xULN (if baseline ALT is <ULN) with symptoms or worsening of acute hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia, OR;
- ALT ≥3x baseline ALT (if baseline ALT is >ULN) with symptoms or worsening of acute hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia;
- ALT ≥5xULN and <8xULN that persists ≥ 2 weeks (with bilirubin <2xULN and no signs or symptoms of acute hepatitis or hypersensitivity);
- ALT ≥5xULN but <8xULN and cannot be monitored weekly for >2 weeks;

Subjects who develop ALT ≥5xULN should be followed weekly until resolution or stabilisation (ALT <5xULN on 2 consecutive evaluations).

When a liver chemistry stopping criterion is met, do the following:

- Immediately hold IP;
- Report the event to the medical monitor within 24 hours of learning its occurrence (see Table 3 and Table 4, Section 6.4.14);
- Complete the liver event eCRF and SAE eCRF, where applicable (see Section 6.4.14);
- Complete the liver imaging and/or liver biopsy eCRFs if these tests are performed;
- Perform liver event follow up assessments (described below), and monitor the subject until liver chemistries resolve, stabilise, or return to baseline values as described below;
- Make every reasonable attempt to have subjects return to clinic within 24 hours for repeat liver chemistries, liver event follow up assessments (see below), and close monitoring;
- A specialist or hepatology consultation is recommended;
- Monitor subjects twice weekly until liver chemistries (ALT, aspartate aminotransferase (AST), alkaline phosphatase, bilirubin) resolve, stabilise or return to within baseline values;

Consider the following additional tests to further evaluate the liver event:

- Viral hepatitis serology including:
  - Hepatitis A IgM antibody;
  - HBsAg and Hepatitis B Core Antibody (IgM);
  - Hepatitis C RNA;
  - Hepatitis E IgM antibody;
- Cytomegalovirus IgM antibody;
- Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
- Syphilis screening;
- Drugs of abuse screen including alcohol;
- Serum acetaminophen test (APAP adduct test). The site must contact GSK when this test is required. Please refer to the SPM.
- Blood sample for pharmacokinetic (PK) analysis, obtained within 60 hours of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of IP prior to blood 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 SPM.

- Serum CPK and lactate dehydrogenase (LDH);
- Fractionate bilirubin, if total bilirubin is greater than 1.5xULN;
- Obtain complete blood count with differential to assess eosinophilia;
- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies;
- Liver imaging (ultrasound, magnetic resonance, or computerised tomography) to evaluate liver disease;
- Record the appearance or worsening of clinical symptoms of hepatitis, 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, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications report form. Record alcohol use on the liver event alcohol intake case report form.

6.4.4.2. Restarting investigational product

Drug Restart/Rechallenge Following Liver Events that are Possibly Related to IP

Approval by the ViiV Safety and Labeling Committee (VSLC) for drug restart can be considered where:

- The subject is receiving compelling benefit, benefit of drug restart exceeds risk, and no effective alternative therapy is available. Ethics Committee or Institutional Review Board approval of drug restart/rechallenge must be obtained, as required.
- If the restart/rechallenge is approved by the VSLC in writing, the subject must be provided with a clear description of the possible benefits and risks of drug administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the IP restart/rechallenge. Documentation of informed consent must be recorded in the study chart.
- Study drug must be administered at the dose specified by the VSLC.
- Subjects approved by the VSLC for rechallenge of IP must return to the clinic twice a week for liver chemistry tests for one month or for as long as clinically indicated and then laboratory monitoring may resume as per protocol.

Refer to Appendix 4, Section 11.4 for further details.

Drug Restart Following Transient Resolving Liver Events Not Related to IP

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

- Liver chemistries have a clear underlying cause (e.g. biliary obstruction, hypotension and liver chemistries have improved to normal or are within 1.5x baseline and

ALT <3xULN). Ethics Committee or Institutional Review Board approval of drug restart/rechallenge must be obtained, as required.

- If restart of drug is approved by the VSLC in writing, the subject must be provided with a clear description of the possible benefits and risks of drug administration, including the possibility of recurrent, more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the restart. Documentation of informed consent must be recorded in the study chart.
- Study drug must be administered at the dose specified by the VSLC.
- Subjects approved by the VSLC for restarting IP must return to the clinic once a week for liver chemistry tests for one month or for as long as clinically indicated and then laboratory monitoring may resume as per protocol. If protocol defined stopping criteria for liver chemistry elevations are met, study drug must be stopped.

Refer to Appendix 4, Section 11.4 for further details.

6.4.4.3. Hypertriglyceridemia/hypercholesterolemia

Samples for lipid measurements must be obtained in a fasted state according to the Time and Events Table (Section 6.1). Subjects who experience **asymptomatic** triglyceride or cholesterol elevations may continue to receive IP.

6.4.4.4. 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 IP, IP should be discontinued and the subject withdrawn from the study.

6.4.4.5. Decline in renal function

Subjects who experience an increase in creatinine from Baseline of 45 µMol/L (or 0.5 mg/dL) should return for a confirmatory assessment within 2 to 4 weeks. A urinalysis and urine albumin/creatinine and urine total protein/albumin ratios should 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 have a decline in the estimated GFR (using the CKD-EPI method) of >50% must return for a confirmatory assessment as soon as possible. A urinalysis and urine albumin/creatinine and urine protein/creatinine ratios should be done at this confirmatory visit. If the estimated GFR has declined by >50% (confirmed), then IP should be withheld and the investigator should contact the study medical monitor to discuss the rationale for restarting study drugs (if appropriate). Consideration for confounding

factors (e.g. background therapy, other medications, dehydration, concurrent conditions) should be taken into account, and a nephrology consult may be obtained. If a subject is also receiving TDF, then a switch to an alternative nucleoside should be considered if restarting IP. One background NRTI change is allowed for management of drug toxicity as described in Section 6.4.4, "Specific Toxicities/Adverse Event Management". If IP is reinitiated, it should have been withheld for no more than 4 weeks. If IP is not reinitiated the subject must be withdrawn.

6.4.4.6. Allergic reaction

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

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

Subjects receiving ABC as part of their NRTI background regimen should be evaluated for the possibility of a clinically suspected ABC hypersensitivity reaction (HSR) and managed appropriately as outlined in the local prescribing information.

6.4.4.7. Rash

Mild to moderate rash is an expected adverse reaction for DTG-containing ART. Episodes generally occur within the first ten weeks of treatment, rarely require interruptions or discontinuations of therapy and tend to resolve within two to three weeks. No instances of serious skin reaction, including SJS, TEN and erythema multiforme, have been reported for DTG in clinical trials. For further characterisation of HSR and rash observed with DTG-containing ART, please see the current version of the IB [GlaxoSmithKline Document Number RM2007/00683/11, GlaxoSmithKline Document Number 2017N352880_00, and GlaxoSmithKline Document Number 2017N352880_01].

TEN, SJS and erythema multiforme have been reported in patients receiving LPV/RTV [Kaletra US Package Insert, 2016; Kaletra EU Summary of Product Characteristics, 2017].

Subjects with an isolated Grade 1 rash may continue IP 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 worsen, or if mucosal involvement develops.

Subjects may continue IP for an isolated Grade 2 rash. However, IP (and all other concurrent medication(s) suspected in the Investigators causality assessment) should be permanently discontinued for any Grade ≥2 rash that is associated with an increase in ALT (see Section 6.4.4.1). 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 IP (and all other concurrent medication(s) suspected in the Investigators causality assessment) for an isolated Grade 3 or 4 rash, and the subject should be withdrawn from the study. Subjects should be treated as clinically appropriate and followed until resolution of the AE.

The rash and any associated symptoms should be reported as adverse events (see Section 6.4.5) and appropriate toxicity ratings should be used to grade the events (see Appendix 3, Section 11.3).

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

Subjects receiving ABC as part of their NRTI background regimen should be evaluated for the possibility of a clinically suspected ABC HSR and managed appropriately as outlined in the local prescribing information.

6.4.5. Adverse Events

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

6.4.5.1. Definition of an AE

Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Events meeting the definition of an AE include:

- 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 that **do not** meet the definition of an AE include:

- 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
- 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

6.4.5.2. Definition of an SAE

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

   Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalisation or prolongation of existing hospitalisation

   Note: In general, hospitalisation signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious.

   Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity, or

   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. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

g. All events of possible drug-induced liver injury with hyperbilirubinaemia defined as ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct) (or ALT ≥ 3xULN and INR>1.5, if INR measured) termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants).

   Note: bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥ 2xULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

Reporting of ABC Hypersensitivity Reactions

If a clinically suspected case of HSR to ABC develops in subjects receiving ABC as part of their NRTI background regimen, and meets one of the International Conference on Harmonization (ICH)-E2A definitions of seriousness listed above, then, in addition to reporting the case as an SAE, the ABC HSR CRF should also be completed within one week of the onset of the hypersensitivity reaction (see Section 6.4.14).

6.4.6. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. ECGs, radiological scans, vital signs measurements), including those that worsen from Baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator are to be recorded as AEs or SAEs. However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are **not** to be reported as AEs or SAEs.

Additionally, diagnostic test results that represent a sign of a clinical condition that is already reported as an AE need not be reported as this would be redundant.

It is important to note that grading for laboratory abnormalities (see Section 11.3) is an objective assessment conducted at the central laboratory (or a laboratory contracted by the central laboratory) and does not translate directly into similarly graded AEs.

6.4.7. Cardiovascular Events

Investigators will be required to fill out event specific data collection tools for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularisation

This information should be recorded in the specific cardiovascular eCRF within one week of when the AE/SAE(s) are first reported.

6.4.8. Death Events

In addition, all deaths will require a specific death data collection tool to be completed. The death data collection tool includes questions regarding cardiovascular (including sudden cardiac death) and noncardiovascular death.

This information should be recorded in the specific death eCRF within one week of when the death is first reported.

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

The events or outcomes listed in the CDC Classification System for HIV-1 Infections (Appendix 2, Section 11.2 [CDC, 1992]) will be recorded on the HIV Associated Conditions CRF 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 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 6.4.5.2), 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.

6.4.10. Suicidality Monitoring

Patients with HIV infection may occasionally present with symptoms of depression and/or suicidality (suicidal ideation or behaviour). In addition, there have been some reports of depression, suicidal ideation and behaviour (particularly in patients with a pre-existing history of depression or psychiatric illness) in some patients being treated with 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 behaviour or any other unusual changes in behaviour. It is recommended that the Investigator consider mental health consultation or referral for subjects who experience signs of suicidal ideation or behaviour. Subjects presenting with new onset/treatment-emergent depression should be advised to contact the investigator immediately if symptoms of severe acute depression (including suicidal ideation/attempts) develop, because medical intervention and discontinuation of the study medication may be required.

Assessment of treatment emergent suicidality will be monitored during this study using the Columbia Suicide Severity Rating Scale (C-SSRS). The definitions of behavioural suicidal events used in this scale are based on those used in the Columbia Suicide History Form [Oquendo, 2003]. Questions are asked on suicidal behaviour, suicidal ideation and intensity of ideation. Day 1 (Baseline) visit questions will be in relation to lifetime experiences and current experiences (within the past 2 months) and all subsequent questioning in relation to the last assessment. The C-SSRS is to be administered as a patient completed questionnaire at the time-points specified in Section 6.1.

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

6.4.11. Pregnancy

6.4.11.1. Pregnancy testing

Women of childbearing potential must have a negative pregnancy test at Screening and Day 1 to be eligible for administration of IP. Pregnancy testing will also be conducted as per the Time and Events Table (see Section 6.1) and at anytime during the trial when pregnancy is suspected.

Additionally, a pregnancy test should also be performed prior to study drug re-administration, when administration is disrupted for more than 7 days (e.g. temporary interruption of study drug).

6.4.11.2. Action to be taken if pregnancy occurs

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

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to GSK within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

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 promptly reported to GSK.

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

6.4.11.3. Time period for collecting pregnancy information

Information on the occurrence of pregnancies in female subjects will be collected over the period starting at Screening and ending at the final on-study or Follow-up visit. Only those pregnancies that occur following the first dose of IP will be reported to GSK. Follow-up information will only be collected for pregnancies occurring from Day 1 to the final on-study or Follow-up visit.

6.4.12. Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

AEs will be collected from the start of study treatment and until the follow up contact.

SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed **as related** to study participation (e.g. study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication, will be recorded from the time a subject consents to participate in the study up to and including any follow up contact. All SAEs will be reported to GSK within 24 hours, as indicated in Section 6.4.14.

6.4.13. Method of Detecting AEs and SAEs

Care must 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?"

6.4.14. Prompt Reporting of Serious Adverse Events and Other Events to GSK

SAEs, pregnancies, and liver function abnormalities meeting pre-defined criteria will be reported promptly by the investigator to GSK as described in Table 3 and Table 4 once the investigator determines that the event meets the protocol definition for that event.

Table 3 Events and Reporting Time Periods for SAEs

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	"SAE" data collection tool	24 hours	Updated "SAE" data collection tool
ALT≥3xULN **and** Bilirubin≥2xULN (>35% direct)	24 hours[1]	"SAE" data collection tool. "Liver Event CRF" and "Liver Imaging" and/or "Liver Biopsy" CRFs, if applicable[2]	24 hours	Updated "SAE" data collection tool/"Liver Event" Documents[2]

1. GSK must be contacted at onset of liver chemistry elevations to discuss subject safety
2. Liver Event Documents (i.e. "Liver Event CRF" and "Liver Imaging CRF" and/or "Liver Biopsy CRF", as applicable) should be completed as soon as possible.

Table 4 Other Events Requiring Prompt Reporting

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
Cardiovascular or death event	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	"CV events" and/or "death" data collection tool(s) if applicable	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	Updated "CV events" and/or "death" data collection tool(s) if applicable
Suspected ABC HSR[1]	1 week	ABC HSR CRF	1 week	Updated ABC HSR CRF
Pregnancy	2 weeks	"Pregnancy Notification Form"	2 weeks	"Pregnancy Follow-up Form"
ALT ≥5xULN and <8xULN that persists ≥2 weeks	24 hours[2]	Liver Event CRF[3]	24 hours	Updated Liver Event CRF[3]
ALT ≥8xULN	24 hours[2]	Liver Event CRF[3]	24 hours	Updated Liver Event CRF[3]
ALT ≥3xULN (if baseline ALT ≤ULN) or ALT ≥3 fold increase from baseline value (if baseline ALT >ULN) with appearance or worsening of symptoms of hepatitis or hypersensitivity	24 hours[2]	Liver Event CRF[3]	24 hours	Updated Liver Event CRF[3]

1. ABC HSR CRF required only if event meets one of the ICH-E2A definitions of 'seriousness'.
2. GSK must be contacted at onset of liver chemistry elevations to discuss subject safety
3. Liver Event Documents (i.e. "Liver Event CRF" and "Liver Imaging CRF" and/or "Liver Biopsy CRF", as applicable) should be completed as soon as possible.

The method of recording, evaluating and follow-up of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in the SPM. Procedures for post-study AEs/SAEs are provided in the SPM.

6.4.14.1. Regulatory reporting requirements for SAEs

Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK 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 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 GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

6.4.15. Other Safety Outcomes

Laboratory Assessments

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

If required for cardiovascular events, additional specific local laboratory assessments will be recorded in the specific cardiovascular eCRF (see Section 6.4.7).

6.5. Health Outcomes

Health outcomes assessments will be conducted in all countries according the schedule in the Time and Events Table (Section 6.1). Assessments are recommended to be administered at the beginning of the visit.

HIVTSQ: The HIV treatment satisfaction questionnaire status version (HIVTSQs) and HIVTSQ change version (HIVTSQc) are self-reported scales that measure overall satisfaction with treatment and by specific domains, e.g. convenience, flexibility [Woodcock, 2001; Woodcock, 2006]. The change version of the HIVTSQ was developed to overcome ceiling effects (i.e. where respondents score maximum or near-maximum satisfaction at Baseline and can show little or no improvement at follow-up. The HIVTSQ will be administered as a paper questionnaire.

MMAS-8: The Morisky 8-Item Medication Adherence Scale (MMAS-8) is a self-report measure of medication-taking behaviour and addresses barriers to medication-taking [Morisky, 2008]. The MMAS-8 will be administered as a paper questionnaire.

GSRS: The Gastrointestinal Symptom Rating Scale (GSRS) is a disease-specific instrument of 15 items combined into five symptom clusters depicting Reflux, Abdominal pain, Indigestion, Diarrhoea and Constipation [Svedlund, 1988]. The GSRS will be administered as a paper questionnaire.

6.5.1. Health Outcome Endpoints

- Change from Baseline, using the Gastrointestinal Symptom Rating Scale (GSRS), at Week 4, Week 24, and Week 48;
- Change from Baseline in treatment satisfaction, using the HIV-Treatment Satisfaction Questionnaire (HIVTSQ), at Week 4, Week 24, and Week 48;
- Change from Baseline in adherence with treatment, using the Morisky 8-Item Medication Adherence Scale (MMAS-8), at Week 4, Week 24, and Week 48.

6.6. Viral Genotyping and Phenotyping

Whole venous blood samples will be obtained from each subject for Screening resistance testing at the central laboratory (or a laboratory contracted by the central laboratory) and on study 'plasma for storage' samples according to the Time and Events Schedule in Section 6.1 for viral genotypic and phenotypic analyses as required.

Details concerning the handling, labelling and shipping of these samples will be supplied separately. Screening viral genotype will be performed through Quest Diagnostics as well as at location(s) to be described in the SPM. Genotypic and phenotypic analyses may be carried out by Monogram Biosciences using, but not limited to, their Standard Phenosense and GenoSure testing methods for protease (PRO) and reverse transcriptase (RT) and Integrase assays. In addition, where Monogram Biosciences resistance testing is not possible, resistance testing may also be performed at location(s) to be described in the SPM.

Screening will include only viral genotype for eligibility determination and to guide the choice of NRTIs.

6.6.1. Virology Endpoint

- Incidence of treatment-emergent genotypic and phenotypic resistance to DTG, LPV/RTV and other on-study ART in subjects meeting confirmed virologic withdrawal criteria.

6.6.2. HIV-1 Pol Viral Genotyping and Phenotyping

Subjects meeting a 'confirmed virologic withdrawal criterion' (see Section 4.6.3) will have plasma samples tested for HIV-1 PRO and RT genotype and phenotype and HIV-1 integrase genotype and phenotype from both Baseline samples and from samples collected at the time of meeting a 'suspected virologic withdrawal criterion'; these results will be reported to the Investigator as soon as available to provide guidance for election of an alternative regimen.

HIV-1 PRO and RT genotype and phenotype will also be determined on the Baseline isolates from all subjects, if possible. When samples cannot be analysed by Monogram Biosciences, Baseline isolate resistance testing may be performed at location(s) to be described in the SPM.

6.6.3. HIV-1 Exploratory Analysis

Additional analyses for HIV-1 resistance may, for example, be carried out on peripheral blood mononuclear cell (PBMC) samples collected at Baseline and/or on stored plasma samples from Baseline and 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 Baseline and the last on-treatment isolates from subjects who have HIV-1 RNA ≥400 c/mL regardless of confirmatory HIV-1 RNA.

6.7. Pharmacogenetic Research

Information regarding pharmacogenetic (PGx) research is included in Appendix 5, Section 11.5.

The IEC/IRB and, where required, the applicable regulatory agency must approve the PGx assessments before these can be conducted at the site. The approval(s) must be in writing and will clearly specify approval of the PGx assessments (i.e. approval of Appendix 5, Section 11.5). In some cases, approval of the PGx assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the PGx assessments is being deferred and the study, except for PGx assessments, can be initiated. When PGx assessments will not be approved, then the approval for the rest of the study will clearly indicate this and therefore, PGx assessments will not be conducted.

7. DATA MANAGEMENT

For this study, subject data will be entered into GSK defined eCRFs, 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 standards and data cleaning procedures to ensure the integrity of the data, e.g. removing errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using MedDRA and an internal validated medication dictionary, GSKDrug. eCRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. In all cases, subject initials will not be collected or transmitted to GSK according to GSK policy.

8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

8.1. Hypotheses

This study is designed to show that the antiviral effect of a regimen of DTG (administered once daily) + two NRTIs is non-inferior to LPV/RTV + two NRTIs.

If r_d is the response rate on DTG + two NRTIs and r_a is the response rate on LPV/RTV + two NRTIs then the hypotheses can be written as follows:

H0: $r_d - r_a \leq -12\%$ H1: $r_d - r_a > -12\%$.

8.2. Study Design Considerations

8.2.1. Sample Size Assumptions

Rationale for non-inferiority margin

The non-inferiority margin of 12% was chosen based on historical data from well-controlled superiority trials in treatment naïve subjects which established a large quantitative contribution to viral suppression of a PI when added as a third drug to a dual NRTI background (approximately 45% using the lower confidence bounds) and the negligible viral load response (less than 5%) in regimens containing dual NRTIs alone [HHS, 2013]. In second-line therapy, the efficacy of optimised dual NRTI alone would be expected to be similar or worse than that seen in treatment naïve studies in light of possible emergence of resistance to NRTIs during virologic failure with first line therapy. Therefore, a non-inferiority margin of 12% is an acceptable margin since it is well below the expected treatment effect for LPV/RTV plus two NRTIs vs. two NRTIs alone.

Response rate assumptions

There are limited randomised prospective study data to indicate response rates of patients receiving second line treatment. Retrospective and cohort analyses of LPV/RTV containing regimens in treatment experienced patients have showed responses between 56.4% and 85.7% at 48 weeks. These studies mostly contained small numbers of patients and differed in their use of backbone agents and the degree of treatment experience of subjects.

The estimated treatment response rate chosen for the comparator (70%) is based on the results from comparable studies of second line ART and the most recent relevant studies of DTG and LPV/RTV in patient population with treatment experience greater than second-line ART.

Studies evaluating second-line therapy

- HIV STAR was a study conducted in Thailand (n=195, ITT) to compare LPV/RTV + TDF/FTC with LPV/RTV monotherapy in patients failing initial therapy on an NNRTI + two NRTI regimen [Bunupuradah, 2012]. In this trial, the primary endpoint of non-inferiority according to mean reduction in HIV RNA from Baseline

over 48 weeks was met with a 1.89 log decrease for the LPV/RTV +TDF/FTC arm compared with a decrease of 1.74 log in the monotherapy arm (difference: 0.15 log; 95% CI: 0.04 to 0.33). For the secondary outcome of proportion of subjects <50 c/mL a lower response was seen for the monotherapy arm. In this analysis, 83% of subjects achieved HIV-1 RNA <50 c/mL (ITT) at Week 48 in the triple therapy arm compared with 61% in the LPV/RTV monotherapy arm (difference: -22.2%, 95% CI -33.5 to -9.0, p <0.01) based on a missing equals failure imputation. As noted in the above manuscript, the high virologic suppression rate in the LPV + TDF/FTC arm may not be applicable to those with a much more extensive duration of NNRTI-based failure. For the LPV + TDF/FTC, the median (IQR) duration of NNRTI-based HAART before enrolment was 2.3 years (1.2-4.0).

- The SECOND LINE study compares the antiviral efficacy of second-line ART comprising LPV/RTV + 2-3 NRTIs with LPV/RTV + RAL, as measured by the proportion of participants with plasma HIV-1 RNA <200 c/mL at Week 48 (n=541) [SECOND-LINE Study Group, 2013]. In this study, the LPV/RTV + RAL arm was found to be non-inferior to LPV/RTV + NRTIs at 48 weeks with 82.6% vs. 80.8% of patients respectively, achieving HIV-1 RNA <200 c/mL (mITT, p=0.59). Similarly, 71.1% and 70.5% of participants achieved an HIV-1 RNA <50 c/mL (mITT, p=0.87) [**Note:** NC=F analysis or Snapshot equivalent showed 68.1% (184/270) vs 66.4% (180/271) of patients achieved HIV-1 RNA <50 c/mL at Week 48]. For the LPV/RTV + 2-3 NRTIs arm, the median (IQR) duration of NNRTI-based HAART before enrolment was 3.3 years (1.8-5.4) years.
- The EARNEST study (ongoing, n=1270), conducted in sub-Saharan Africa was powered on **75%** for the composite endpoint of 'good HIV disease control' at Week 96. At Week 96, 74% achieved HIV-1 RNA <50 c/mL with LPV/r + 2-3 NRTIs [Paton, 2013].

Studies in more treatment experienced populations

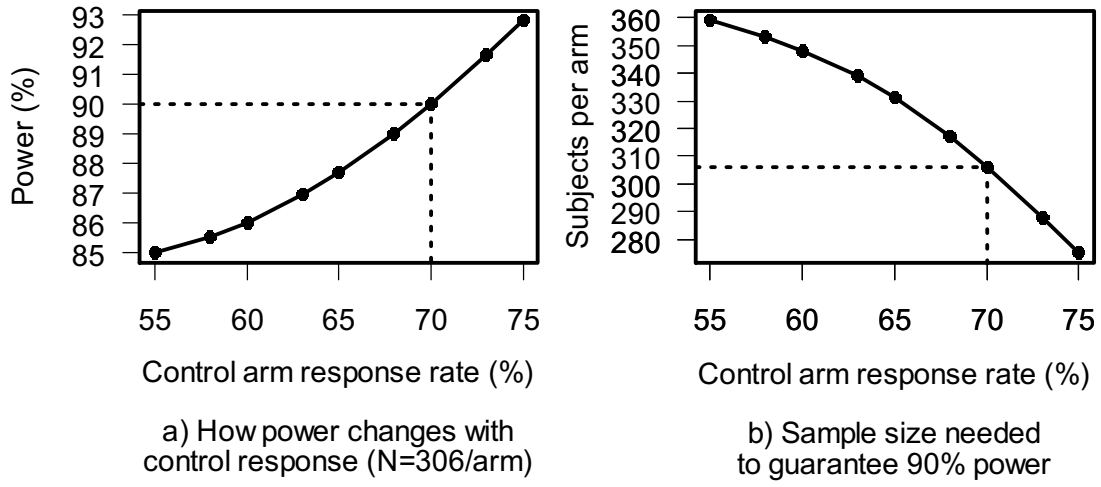
- The TITAN study (LPV/RTV vs DRV+RTV): the response rate for LPV/RTV arm was **68%** (< 50 c/mL at 48 weeks, n=595) [Madruga, 2007]. This study population was more treatment experienced than the current study, with 47% of subjects having prior 3-class experience (NRTI + NNRTI + PI).
- The SAILING study (DTG vs RAL): in subjects receiving DTG in combination with 1-2 investigator-selected background agents, the proportion of subjects with plasma HIV-1 RNA < 50 c/mL at Week 48 (Snapshot) was 71% (251/354) [Cahn, 2013]. This study population had documented genotypic or phenotypic resistance to at least one member of each of at least two ART drug classes (NRTI, NNRTI, PI, fusion or entry inhibitor).

This study will randomise at least 306 subjects per arm. Assuming a true response rate of 70% in each arm, this sample size will provide 90% power to show non-inferiority for the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 with a 12% non-inferiority margin and a one-sided 2.5% significance level. If we observe a 70% response rate in the LPV arm then non-inferiority would be declared if the observed treatment difference (DTG - LPV) was better than -4.6 percentage points.

8.2.2. Sample Size Sensitivity

Figure 2 shows the sensitivity of the required sample size to the true response rate for the control arm (assuming no true difference between arms). Assuming identical response rates in each arm, if the true response rate is as low as 65%, the study will still have 88% power to meet its primary objective. In this case, an extra 50 subjects (25 per arm) would be required to restore 90% power.

Figure 2 Sample Size Sensitivity



8.2.3. Sample Size Re-estimation

No sample size re-estimation is planned for this study.

8.3. Data Analysis Considerations

8.3.1. Analysis Populations

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

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

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

Safety Population

The Safety Population is defined as all subjects who receive at least one dose of IP. Subjects will be analyzed according to the actual treatments received.

Per-Protocol Population

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

ITT Population (ITT)

This population will consist of all randomised subjects. Subjects will be assessed according to their randomised treatment even if no study treatment was taken or the wrong treatment was received. The ITT population will be used for sensitivity analyses of the primary efficacy endpoint.

8.3.2. Analysis Data Sets

For the primary efficacy analysis, each subjects responses (e.g. <50 c/mL) will be calculated according to the FDA's Snapshot algorithm. This algorithm treats all subjects without HIV 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 as follows:

- Background ART substitutions not permitted per protocol;
- Background ART substitutions permitted per protocol after Week 4 (or date of first on-treatment viral load collection, if earlier) where the last HIV-1 RNA result prior to the date of decision to switch is ≥50 c/mL.

  Note: if the last HIV-1 RNA result prior to the date of decision to switch is <50 c/mL then the permitted change in background ART will have no effect on the analysis.

Note: A switch from 3TC to FTC (or vice versa) will not be considered a background NRTI change and will not incur a penalty in the Snapshot algorithm, regardless of reason or date of switch, as these agents are assumed to be of equal efficacy.

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 on this Snapshot algorithm will be contained in the RAP.

The observed case (OC) dataset, which uses only data that is 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.

Full details on methods to address missing data for secondary efficacy and health outcomes endpoints will be discussed in the RAP.

8.3.3. Treatment Comparisons

8.3.3.1. Primary comparisons of interest

The primary analysis will be based on the ITT-E population using the Snapshot dataset. The primary comparison will be made at a one-sided 2.5% level of significance. Treatment with DTG + two NRTIs will be declared non-inferior to treatment with LPV/RTV + two NRTIs if the lower end of a two-sided 95% confidence interval for the difference between the two groups in response rates at Week 48 lies above -12%.

8.3.3.2. Other comparisons of interest

The analysis described above in Section 8.3.3.1 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 + two NRTIs is superior to treatment with LPV/RTV + two NRTIs will be tested using the same level of significance as for the tests of non-inferiority. Superiority will be declared if the lower end of the confidence internal is above 0%. The primary comparison will also be performed using the ITT population and will be compared for consistency with the results from the ITT-E and PP populations.

The supportive analysis using the ITT population will classify subjects randomised but not exposed to study treatment as non-responders and therefore conservatively addresses any selection bias that may occur given the open-label study design.

8.3.3.3. Secondary comparisons

The following key secondary comparisons will be tested:

- Superiority of DTG + two NRTIs compared to LPV/RTV + two NRTIs with respect to change from Baseline in fasting LDL cholesterol at Week 48 using the Safety population;

- Superiority of DTG + two NRTIs compared to LPV/RTV + two NRTIs with respect to the incidence of maximum post-Baseline emergent Grade 2 or greater laboratory abnormalities in fasting LDL cholesterol by Week 48 using the Safety population;

- Superiority of DTG + two NRTIs compared to LPV/RTV + two NRTIs with respect to change from Baseline in fasting TC/HDL ratio at Week 48 using the Safety population;

- Superiority of DTG + two NRTIs compared to LPV/RTV + two NRTIs with respect to the incidence of maximum post-Baseline emergent Grade 2 or greater drug-related diarrhoea by Week 48 using the Safety population;

- Proportion of subjects without virologic or tolerability failure by Weeks 24 and 48, where failure equals treatment-related discontinuation (meeting confirmed virologic withdrawal criteria, treatment-related adverse event, safety stopping criteria, and lack of efficacy);

- Superiority of DTG + two NRTIs compared to LPV/RTV + two NRTIs with respect to time to viral suppression (HIV-1 RNA <50 c/mL) using ITT-E population.

8.3.4. Interim Analysis

The main analysis will be conducted to evaluate the primary objective of the protocol when all subjects have completed their Week 52 visit.

8.3.4.1. Week 24 data cut

An interim analysis will be conducted when all subjects have completed their Week 24 visit in order to provide an earlier assessment of efficacy to inform the Sponsor and clinicians. The analyses described in Section 8.3.3 and Section 8.3.5 will be performed with the sole difference being that the timepoint for these analyses will be Week 24 instead of Week 48.

No adjustment for multiplicity will be made for this analysis because the Week 24 endpoints represent secondary objectives for the study which are subordinate to the primary analysis at Week 48.

8.3.4.2. IDMC interim analyses

An IDMC has been instituted to provide independent review of the accumulating data, primarily to ensure subjects are not being sub-optimally treated in either arm.

Three formal interim analyses were planned for review by the IDMC (Table 5).

Table 5 Timing of Planned IDMC Interim Analyses and Statistical Stopping Guidelines

Interim Analysis	Timing	Endpoint	Evaluation (guideline)
#1	Once 100 subjects (total) have completed their Week 16 visit	Proportion of subjects with HIV-1 RNA <50 c/mL at Week 16 (Snapshot algorithm)	• Inferiority[a] (one-sided p<0.01)
#2	Once 300 subjects (total) have completed their Week 24 visit	Proportion of subjects with HIV-1 RNA <50 c/mL at Week 24 (Snapshot algorithm)	• Inferiority[a] (one-sided p<0.01)
#3	Once all subjects have completed their Week 24 visit	Proportion of subjects with HIV-1 RNA <50 c/mL at Week 48 (Snapshot algorithm)	• Inferiority[a] (one-sided p<0.01) • Superiority[b] (one-sided p<0.0001)

a. Inferiority: significantly lower response rate with DTG than LPV/r.
b. Superiority: significantly higher response rate with DTG than LPV/r.

It is intended that the second interim analysis will occur roughly halfway between the second and third interim analyses, although this will be affected by the actual rate of study recruitment.

The third interim analysis will occur after all subjects have completed Week 24, but the stopping guideline is provided for the proportion of subjects with suppression at Week 48 (including all subjects randomised at least 48 weeks prior to the last subject completing Week 24). For this reason, the number of subjects with week 48 data at the third interim analysis cannot be specified in advance.

The IDMC completed interim analyses #1 and #2. Prior to interim analysis #3, the IDMC conducted an ad hoc review of trial data and observed significant, clinically relevant differences between treatment arms in favour of DTG. The IDMC recommended to the sponsor that the LPV/RTV treatment arm be discontinued and subjects currently receiving LPV/RTV in the study be switched to a regimen with DTG as the third drug, if considered appropriate by the Investigator. Interim analysis #3 will no longer take place.

Stopping Guidelines

Proposed p-value boundaries that may lead to an IDMC recommendation to stop the study at each interim analysis are provided in Table 5. These have been provided as a guide only, with the expectation that the IDMC will base its recommendation to stop or continue the study based on all available evidence and the IDMC's collective judgment. This stopping guidance is not a substitute for the medical, scientific or statistical expertise of the IDMC. Moreover, if a guideline boundary is crossed then the IDMC will be asked to undertake a thorough review of the data, including all available data on treatment- and efficacy-related discontinuations (discontinuations due to virologic failure, lack of efficacy, drug-related adverse events), viral load data at all timepoints, and response by number of fully active background NRTIs.

Formal assessments of inferiority will be conducted at each interim analysis. Inferiority for this study is defined as evidence that DTG has a substantially lower response rate than LPV. A statistical guideline of $p<0.01$ (one-sided) will be used for each inferiority evaluation.

A formal assessment for superiority will be conducted only at the third interim analysis. Superiority is defined as substantial evidence that DTG has a higher response rate than LPV. A statistical guideline of $p<0.0001$ (one-sided) will be used for this evaluation of DTG superiority.

No adjustment for multiple comparisons will be made since the impact of these guidelines do not alter the Type I error rate in favour of DTG to any measurable degree (Table 6).

The analysis method for these comparisons will be the same as that used in the final primary analysis (i.e. adjusted difference in proportion based on stratified analysis).

The statistical properties of the proposed stopping guidelines are explored below. For illustrative purposes only, the p-value boundaries are assumed to be binding (i.e. if crossed the study must be stopped). However, in practice, the p-value boundaries are not binding and are to be used as guides only: signaling that additional exploration of the data is warranted, as described previously.

Table 6 presents simulated probabilities of crossing the p-value boundaries at each interim analysis, and for declaring non-inferiority/superiority at the final primary Week 48 analysis.

Table 6 Probability of crossing boundary at each analysis time-point for the ITT-E population

Interim Analysis	Week 48 True treatment effect= -12% (null hypothesis)			Week 48 True treatment effect = 0% (alternative hypothesis)		
	Inferiority	Superiority	Non-inferiority	Inferiority	Superiority	Non-inferiority
1	5.02%	-	-	1.18%	-	-
2	13.3%	-	-	0.97%	-	-
3	30.3%	0	-	0.89%	0.01%	-
Final	-	0	2.35%	-	2.49%	88.2%

When the true treatment difference is -12% (i.e. under the null hypothesis that DTG is inferior to LPV), the probability of wrongfully claiming non-inferiority is estimated to be 2.35%, which is conservatively below the desired false positive error of 2.5%. The probability that the inferiority boundary will be crossed at any one of the three interim analyses is estimated to be 49%.

When the true treatment effect is 0% (i.e. under the alternative hypothesis that both arms have response rates of 70%), the probability to correctly claim non-inferiority (i.e. power) is estimated to be 88.2%, slightly below the planned 90% level. The probability that an inferiority boundary will be wrongfully crossed at any one of the three interim analyses is estimated to be 3%. The probability that the superiority boundary will be crossed at the third interim analysis is 0.01% and 2.49% at the final analysis, if the true population response rate is 70% in each arm.

The unblinded interim analysis will be performed and delivered to the IDMC by an independent Statistics Data Analysis Centre (SDAC) external to the sponsor, so that the IDMC is able to evaluate the questions described in the committee charter. The IDMC will review the list of data to be assessed and potentially may decide to review other types of data. Further details regarding the operation of the IDMC, the use of a SDAC for generating unblinded data, and content of the reviews are described in the charter.

8.3.5. Key Elements of Analysis Plan

The study design is open-label; however, the sponsor staff 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 interim Week 24 analysis.

8.3.5.1. Efficacy analyses

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

statistical analysis, 4 strata (subgroups) will be formed according to the combinations of levels of the following categorical variables:

- Baseline plasma HIV-1 RNA (≤ vs. >100,000 c/mL);
- Number of fully active background NRTIs (<2 vs. 2) at Baseline.

For analysis purposes, fully active is defined at Baseline by the genotypic resistance reports of the central laboratory (or a laboratory contracted by the central laboratory) showing no evidence of full or of partial genotypic resistance for a given NRTI. If Baseline genotypic results are not available, then activity of the background regimen will be based on genotypic results at Screening.

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 treated subjects, m_k is the number of LPV 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_a, for the *k*th strata.

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

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

using the variance estimator $\hat{\text{var}}(\hat{d}_{cmh})$ 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.

The weighted least squares chi-squared statistic [Fleiss, 1981] will be used to test for one-way homogeneity across the levels of each categorical variable, with each categorical variable considered separately. Following Lui and Kelly [Lui, 2000], ½ will be added to each cell in any strata for which the stratum-specific rate estimates of either r_d or r_a are zero or one, and tests will be one-sided. Full details will be contained in the RAP. 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.

Following the IDMC recommendation to switch LPV/RTV subjects to DTG, additional sensitivity analyses will be conducted for the primary endpoint. Further details of these analyses and any other impacted analyses will be included in the RAP.

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

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).

8.3.5.2. Safety analyses

Exposure to study medication, measured by the number of weeks on study drug, will be summarised by treatment group. The proportion of subjects reporting AEs will be tabulated for each treatment group. The following summaries of AEs will be provided:

- Incidence and severity of all AEs
- Incidence and severity of treatment related AEs
- Incidence and severity of AEs leading to withdrawal
- Incidence of SAEs

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

Further details of safety analyses will be included in the RAP.

8.3.5.3. Health outcomes analyses

HIVTSQ

The HIVTSQ was developed to evaluate treatments for HIV and patient satisfaction [Woodcock, 2001; Woodcock, 2006]. The higher the score, the greater the improvement in treatment satisfaction as compared to the past few weeks. A smaller score represents a decline in treatment satisfaction compared to the past few weeks.

This study will use the 14-item HIVTSQs (status version) and the 14-item HIVTSQc (change version), both including the 10 items of the standard HIVTSQ but having four additional items for testing. These measures will assess change in treatment satisfaction over time (in the same subjects) and compare current satisfaction with previous treatment satisfaction, from an earlier time point.

MMAS-8

The original Morisky Medication Adherence Scale (MMAS) was a four item scale that was developed to assess medication adherence with chronic conditions, such as antihypertensive agents [Morisky, 1986]. More recently, an eight-item self-reported scale was developed called the Morisky 8-Item Medication Adherence Scale (MMAS-8) [Morisky, 2008]. Scores of 8 indicate CCI [redacted], and scores of less than 6 indicate CCI [redacted] on the MMAS-8 scale.

Scores will be summarised and compared between the treatment groups in an exploratory analysis at each time point.

GSRS

The Gastrointestinal Symptom Rating Scale (GSRS) has 15 items and is divided into four domains: abdominal pain; dyspeptic syndrome; indigestion syndrome; and bowel syndrome. The scale ranges from CCI [redacted] (1) to CCI [redacted] (7). The overall score is calculated by adding the completed scores of individual items in each group, for a possible total ranging from 15 to 105. Higher scores show greater severity of symptoms [Svedlund, 1988]. The GSRS has been used and validated in other antiretroviral studies, which examine the GI symptoms associated with boosted PIs [Sáez de la Fuente; 2009; Mtambo, 2013].

Scores will be summarised and compared between the treatment groups in an exploratory analysis at each time point.

8.3.5.4. Viral genotyping/phenotyping analyses

The incidence of treatment emergent genotypic and phenotypic resistance to NRTIs, PIs, and INIs will be summarised by treatment arm for subjects meeting confirmed virologic withdrawal criteria. Details of the analyses to be performed will be specified in the RAP.

8.3.5.5. Pharmacogenetic analyses

See Appendix 5, Section 11.5, for details about the Pharmacogenetics Analysis Plan.

9. STUDY CONDUCT CONSIDERATIONS

9.1. Posting of Information on Publicly Available Clinical Trial Registers

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

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

Prior to initiation of a study site, 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.

The study will be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008, including, but not limited to:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and favourable opinion/approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements.

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

Written informed consent must be obtained from each subject prior to participation in the study.

In approving the clinical protocol the IEC/IRB and, where required, the applicable regulatory agency are also approving the optional assessments e.g. PGx assessments described in Appendix 5 (Section 11.5), unless otherwise indicated. Where permitted by regulatory authorities, approval of the optional assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the optional assessments is being deferred and the study, except for the optional assessments, can be initiated. When the optional assessments are not approved, then the approval for the rest of the study will clearly indicate this and therefore, the optional assessments will not be conducted.

9.3. Quality Control (Study Monitoring)

In accordance with applicable regulations, GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the discussion will include

identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK will monitor the study to ensure 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.

9.4. 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.

9.5. Study and Site Closure

Unless terminated early, this study will be considered completed after the last subject completes the last study-related clinic visit or assessment. Upon completion or termination of the study, the GSK monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, GCP, and GSK Standard Operating Procedures.

GSK reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe non-compliance. If GSK determines that such action is required, GSK will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, GSK will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for **safety reasons**, GSK will promptly inform all investigators, heads of the medical institutions (where applicable),and/or institutions conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

9.6. Records Retention

Following closure of the study, the investigator or 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 easily accessible when needed (e.g. for a 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 the records may be maintained in a format other than hard copy (e.g. microfiche, scanned, electronic); however, caution must 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. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

GSK will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, GSK standard operating procedures, and/or institutional requirements.

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

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

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

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 results summary will be posted to the Clinical Study Register no later than eight months after the final primary completion date, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome. In addition, a manuscript will be submitted to a peer reviewed journal for publication no later than 18 months after the last subject's last visit (LSLV). When manuscript publication in a peer reviewed journal is not feasible, a statement will be added to the register to explain the reason for not publishing.

9.8. Independent Data Monitoring Committee (IDMC)

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. Planned stopping guidelines and schedule for interim analyses are provided in Section 8.3.4.2, with additional details described in the charter, which is available upon request.

The IDMC completed pre-planned interim analyses #1 and #2 and following an ad hoc review of trial data prior to interim analysis #3, the IDMC observed significant, clinically relevant differences between treatment arms in favour of DTG. The IDMC recommended that the LPV/RTV treatment arm be discontinued and subjects currently receiving LPV/RTV in the study be switched to a regimen with DTG as the third drug, if considered appropriate by the Investigator. Interim analysis #3 will no longer take place.

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11. APPENDICES

11.1. Appendix 1: Child-Pugh Classification

A subject is classified with [redacted] (Class A) if their overall sum of scores is 5-6 points, [redacted] (Class B) if their overall sum of scores is 7-9 points, and [redacted] (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 7). For subjects requiring anticoagulation therapy, discussion with the study medical monitor will be required.

Table 7 Child-Pugh System

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

[redacted]

[Pugh, 1973; Lucey, 1997]

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11.2. Appendix 2: CDC Classification System for HIV-1 Infections (1993)

Clinical Categories

The clinical categories of HIV infection are defined as follows:

Category A

Category A consists of one or more of the conditions listed below in an adolescent or adult (>13 years) with documented HIV infection. Conditions listed in Categories B and C must not have occurred.

- Asymptomatic HIV infection
- Persistent generalised lymphadenopathy
- Acute (primary) HIV infection with accompanying illness or history of acute HIV infection

Category B (Symptomatic non-AIDS conditions)

Category B consists of symptomatic conditions in an HIV-infected adolescent or adult that are not included among conditions listed in clinical Category C and that meet at least one of the following criteria: a) the conditions are attributed to HIV infection or are indicative of a defect in cell-mediated immunity; or b) the conditions are considered by physicians to have a clinical course or to require management that is complicated by HIV infection. **Examples** of conditions in clinical Category B include, **but are not limited to:**

- Bacillary angiomatosis
- Candidiasis, oropharyngeal (thrush)
- Candidiasis, vulvovaginal; persistent, frequent, or poorly responsive to therapy
- Cervical dysplasia (moderate or severe)/cervical carcinoma in situ
- Constitutional symptoms, such as fever (38.5°C) or diarrhea lasting >1 month
- Hairy leukoplakia, oral
- Herpes zoster (shingles), involving at least two distinct episodes or more than one dermatome
- Idiopathic thrombocytopenic purpura
- Listeriosis
- Pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess
- Peripheral neuropathy

For classification purposes, Category B conditions take precedence over those in Category A. For example, someone previously treated for oral or persistent vaginal

candidiasis (and who has not developed a Category C disease) but who is now asymptomatic should be classified in clinical Category B.

Category C (AIDS indicator conditions as defined by diagnostic or presumptive measures)

Category C includes the clinical conditions listed in the AIDS surveillance case definition. For classification purposes, once a Category C condition has occurred, the person will remain in Category C.

Conditions in Category C include:

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis, esophageal
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcer(s) (>1 month's duration);or bronchitis, pneumonitis, or esophagitis
- 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 *M. kansasii*, disseminated or extrapulmonary
- Mycobacterium tuberculosis, any site (pulmonary or extrapulmonary)
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis carinii* pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- Salmonella septicaemia, recurrent

- Toxoplasmosis of brain
- Wasting syndrome due to HIV
- Non-CDC, HIV-associated conditions.

Reference

CDC. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR 1992; 41 (No. RR-17):1-19.

11.3. Appendix 3: Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events

VERSION 1.0, DECEMBER 2004; CLARIFICATION AUGUST 2009

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.

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
ESTIMATING SEVERITY GRADE[1]				
Clinical adverse event NOT identified elsewhere in this DAIDS AE grading table	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 Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
SYSTEMIC				
Acute systemic allergic reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic 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
Fatigue Malaise	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 fatigue/malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7 – 38.6°C	38.7 – 39.3°C	39.4 – 40.5°C	> 40.5°C

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Pain (indicate body site) DO NOT use for pain due to injection (See Injection Site Reactions: Injection site pain) See also Headache, Arthralgia, and Myalgia	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 (other than emergency room visit) indicated
Unintentional weight loss	NA	5 – 9% loss in body weight from baseline	10 – 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
INFECTION				
Infection (any other than HIV infection)	Localized, no systemic antimicrobial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antimicrobial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (e.g., septic shock)
INJECTION SITE REACTIONS				
Injection site pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than emergency room visit) indicated for management of pain/tenderness

CLINICAL					
PARAMETER		**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Injection site reaction (localized)					
	Adult > 15 years	Erythema OR Induration of 5x5 cm – 9x9 cm (or 25 cm^2 – 81cm^2)	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2)	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
	Pediatric ≤ 15 Years	Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter	Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (e.g., upper arm/thigh)	Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (e.g., upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Necrosis (involving dermis and deeper tissue)
Pruritis associated with injection See also Skin: Pruritis (itching - no skin lesions)		Itching localized to injection site AND Relieved spontaneously or with < 48 hours treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA
SKIN – DERMATOLOGICAL					
Alopecia		Thinning detectable by study participant (or by caregiver for young children and disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous reaction – rash		Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation		Slight or localized	Marked or generalized	NA	NA
Hypopigmentation		Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)		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

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
CARDIOVASCULAR				
Cardiac arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of $\leq$ 2 units packed RBCs (for children $\leq$ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children >10 cc/kg) indicated
Hypertension				
Adult > 17 years (with repeat testing at same visit)	140 – 159 mmHg systolic OR 90 – 99 mmHg diastolic	160 – 179 mmHg systolic OR 100 – 109 mmHg diastolic	$\geq$180 mmHg systolic OR $\geq$ 110 mmHg diastolic	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Pediatric $\leq$ 17 Years (with repeat testing at same visit)	NA	91st – 94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (e.g., malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life threatening physiologic consequences OR Effusion with non-urgent intervention indicated	Life-threatening consequences (e.g., tamponade) OR Urgent intervention indicated
Prolonged PR interval				
Adult > 16 years	PR interval 0.21 – 0.25 sec	PR interval > 0.25 sec	Type II 2nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
Pediatric $\leq$ 16 Years	1st degree AV block (PR > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Prolonged QTc				
Adult > 16 years	Asymptomatic, QTc interval 0.45-0.47 sec OR Increase interval <0.03 sec above baseline	Asymptomatic, QTc interval 0.48-0.49 sec OR Increase in interval 0.03 – 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, e.g., Torsade de pointes or other associated serious ventricular dysrhythmia
Pediatric ≤ 16 years	Asymptomatic, QTc interval 0.450–0.464 sec	Asymptomatic, QTc interval 0.465-0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, e.g., Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/embolism	NA	Deep vein thrombosis AND No intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (e.g., anticoagulation, lysis filter, invasive procedure)	Embolic event (e.g., pulmonary embolism, life-threatening thrombus)
Vasovagal episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular dysfunction (congestive heart failure)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic congestive heart failure	Life-threatening congestive heart failure
GASTROINTESTINAL				
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [e.g., tube feeding or total parenteral nutrition (TPN)]
Comment: Please note that, while the grading scale provided for Unintentional Weight Loss may be used as a guideline when grading anorexia, this is not a requirement and should not be used as a substitute for clinical judgment.				
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (e.g., diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis or 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)

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Diarrhea				
Adult and Pediatric ≥ 1 year	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 – 6 stools over baseline per 24-hour period	Bloody diarrhea OR Increase of 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
Pediatric < 1 year	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	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake
Mucositis/stomatitis (clinical exam) Indicate site (e.g., larynx, oral) See Genitourinary for Vulvovaginitis See also Dysphagia-Odynophagia and Proctitis	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (e.g., aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 – 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than emergency room visit)	Symptomatic AND Hospitalization indicated (other than emergency room visit)	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Proctitis (functional-symptomatic) Also see Mucositis/stomatitis for clinical exam	Rectal discomfort AND 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)

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting 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)
NEUROLOGIC				
Alteration in personality-behavior or in mood (e.g., agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (e.g., suicidal and homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	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	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions
Cognitive and behavioral/attentional disturbance (including dementia and attention deficit disorder)	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
CNS ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit
Developmental delay – Pediatric ≤ 16 Years	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

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than emergency room visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social & functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weakness causing no or minimal interference with usual social & functional activities	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 (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	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
Seizure: (new onset) – Adult ≥ 18 years See also Seizure: (known pre-existing seizure disorder)	NA	1 seizure	2 – 4 seizures	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)
Seizure: (known pre-existing seizure disorder) – Adult ≥ 18 years For worsening of existing epilepsy the grades should be based on an increase from previous level of control to any of these levels.	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR Infrequent break-through seizures while on stable medication in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (e.g., severity or focality)	Seizures of any kind which are prolonged, repetitive (e.g., status epilepticus), or difficult to control (e.g., refractory epilepsy)

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Seizure – Pediatric < 18 years	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5 – 20 minutes with <24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting >20 minutes	Seizure, generalized onset with or without Secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
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
RESPIRATORY				
Bronchospasm (acute)	FEV1 or peak flow reduced to 70-80%	FEV1 or peak flow 50–69%	FEV1 or peak flow 25–49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or respiratory distress				
Adult ≥ 14 years	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support Indicated
Pediatric < 14 years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 – 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated
MUSCULOSKELETAL				
Arthralgia See also Arthritis	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 See also Arthralgia	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

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Bone Mineral Loss				
Adult ≥ 21 years	BMD t-score -2.5 to -1.0	BMD t-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening Consequences
Pediatric < 21 years	BMD z-score -2.5 to -1.0	BMD z-score < -2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening Consequences
Myalgia (non-injection site)	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	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions
GENITOURINARY				
Cervicitis (symptoms) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	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
Cervicitis (clinical exam) (For use in studies evaluating topical study agents) For other cervicitis see Infection: Infection (any other than HIV infection)	Minimal cervical abnormalities on examination (erythema, Mucopurulent discharge, or friability) OR Epithelial disruption < 25% of total surface	Moderate cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption of 25 – 49% total surface	Severe cervical abnormalities on examination (erythema, mucopurulent discharge, or friability) OR Epithelial disruption 50 – 75% total surface	Epithelial disruption > 75% total surface
Inter-menstrual bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic examination	Inter-menstrual bleeding not greater in duration or amount than usual menstrual cycle	Inter-menstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Urinary tract obstruction (e.g., stone)	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
Vulvovaginitis (symptoms) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	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
Vulvovaginitis (clinical exam) (Use in studies evaluating topical study agents) For other vulvovaginitis see Infection: Infection (any other than HIV infection)	Minimal vaginal abnormalities on examination OR Epithelial disruption <25% of total surface	Moderate vaginal abnormalities on examination OR Epithelial disruption of 25 - 49% total surface	Severe vaginal abnormalities on examination OR Epithelial disruption 50 - 75% total surface	Vaginal perforation OR Epithelial disruption > 75% total surface
OCULAR/VISUAL				
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual changes (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)
ENDOCRINE/METABOLIC				
Abnormal fat accumulation (e.g., back of neck, breasts, abdomen)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes mellitus	NA	New onset without need to initiate medication OR Modification of current medications to regain glucose control	New onset with initiation of medication indicated OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma)

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic 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	Asymptomatic	Symptomatic 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 (e.g., fat loss from the face, extremities, buttocks)	Detectable by study participant (or by caregiver for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

1. **Basic Self-care Functions** – Adult: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.
2. **Basic Self-care Functions** – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).
3. **Usual Social & Functional Activities** – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.
4. **Usual Social & Functional Activities** – Young Children: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.).

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
HEMATOLOGY	***Standard International Units are listed in italics***			
Absolute CD4+ count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	300 – 400/mm^3 *300 – 400/µL*	200 – 299/mm^3 *200 – 299/µL*	100 – 199/mm^3 *100 – 199/µL*	< 100/mm^3 *< 100/µL*
Absolute lymphocyte count **– Adult and Pediatric > 13 years** (HIV NEGATIVE ONLY)	600 – 650/mm^3 *0.600 x 10^9 – 0.650 x 10^9/L*	500 – 599/mm^3 *0.500 x 10^9 – 0.599 x 10^9/L*	350 – 499/mm^3 *0.350 x 10^9 – 0.499 x 10^9/L*	< 350/mm^3 *< 0.350 x 10^9/L*
Comment: Values in children ≤ 13 years are not given for the two parameters above because the absolute counts are variable.				
Absolute neutrophil count (ANC)				
Adult and Pediatric, > 7 days	1,000 – 1,300/mm^3 *1.000 x 10^9 – 1.300 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	500 – 749/mm^3 *0.500 x 10^9 – 0.749 x 10^9/L*	< 500/mm^3 *< 0.500 x 10^9/L*
Infant*†, 2 – ≤ 7 days	1,250 – 1,500/mm^3 *1.250 x 10^9 – 1.500 x 10^9/L*	1,000 – 1,249/mm^3 *1.000 x 10^9 – 1.249 x 10^9/L*	750 – 999/mm^3 *0.750 x 10^9 – 0.999 x 10^9/L*	< 750/mm^3 *< 0.750 x 10^9/L*
Infant*†, ≤1 day	4,000 – 5,000/mm^3 *4.000 x 10^9 – 5.000 x 10^9/L*	3,000 – 3,999/mm^3 *3.000 x 10^9 – 3.999 x10^9/L*	1,500 – 2,999/mm^3 *1.500 x 10^9 – 2.999 x 10^9/L*	< 1,500/mm^3 *< 1.500 x 10^9/L*
Fibrinogen, decreased	100 – 200 mg/dL *1.00 – 2.00 g/L* OR 0.75 – 0.99 x LLN	75 – 99 mg/dL *0.75 – 0.99 g/L* OR 0.50 – 0.74 x LLN	50 – 74 mg/dL *0.50 – 0.74 g/L* OR 0.25 – 0.49 x LLN	< 50 mg/dL *< 0.50 g/L* OR < 0.25 x LLN OR Associated with gross bleeding

LABORATORY				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Hemoglobin (Hgb)				
Adult and Pediatric ≥ 57 days (HIV POSITIVE ONLY)	8.5 – 10.0 g/dL *5.24 – 6.23 mmol/L*	7.5 – 8.4 g/dL *4.62 – 5.23 mmol/L*	6.50 – 7.4 g/dL *4.03 – 4.61 mmol/L*	< 6.5 g/dL *< 4.03 mmol/L*
Adult and Pediatric ≥ 57 days (HIV NEGATIVE ONLY)	10.0 – 10.9 g/dL *6.18 – 6.79 mmol/L* OR Any decrease 2.5 – 3.4 g/dL *1.58 – 2.13 mmol/L*	9.0 – 9.9 g/dL *5.55 – 6.17 mmol/L* OR Any decrease 3.5 – 4.4 g/dL *2.14 – 2.78 mmol/L*	7.0 – 8.9 g/dL *4.34 – 5.54 mmol/L* OR Any decrease ≥ 4.5 g/dL *≥ 2.79 mmol/L*	< 7.0 g/dL *< 4.34 mmol/L*
Infant*†, 36 – 56 days (HIV POSITIVE OR NEGATIVE)	8.5 – 9.4 g/dL *5.24 – 5.86 mmol/L*	7.0 – 8.4 g/dL *4.31 – 5.23 mmol/L*	6.0 – 6.9 g/dL *3.72 – 4.30 mmol/L*	< 6.00 g/dL *< 3.72 mmol/L*
Infant*†, 22 – 35 days (HIV POSITIVE OR NEGATIVE)	9.5 – 10.5 g/dL *5.87 – 6.54 mmol/L*	8.0 – 9.4 g/dL *4.93 – 5.86 mmol/L*	7.0 – 7.9 g/dL *4.34 – 4.92 mmol/L*	< 7.00 g/dL *< 4.34 mmol/L*
Infant*†, ≤21 days (HIV POSITIVE OR NEGATIVE)	12.0 – 13.0 g/dL *7.42 – 8.09 mmol/L*	10.0 – 11.9 g/dL *6.18 – 7.41 mmol/L*	9.0 – 9.9 g/dL *5.59 – 6.17 mmol/L*	< 9.0 g/dL *< 5.59 mmol/L*
International Normalized Ratio of prothrombin time (INR)	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 3.0 x ULN	> 3.0 x ULN
Methemoglobin	5.0 – 10.0%	10.1 – 15.0%	15.1 – 20.0%	> 20.0%
Prothrombin Time (PT)	1.1 – 1.25 x ULN	1.26 – 1.50 x ULN	1.51 – 3.00 x ULN	> 3.00 x ULN
Partial Thromboplastin Time (PTT)	1.1 – 1.66 x ULN	1.67 – 2.33 x ULN	2.34 – 3.00 x ULN	> 3.00 x ULN
Platelets, decreased	100,000 – 124,999/mm^3 *100.000 x 10^9 – 124.999 x 10^9/L*	50,000 – 99,999/mm^3 *50.000 x 10^9 – 99.999 x 10^9/L*	25,000 – 49,999/mm^3 *25.000 x 10^9 – 49.999 x 10^9/L*	< 25,000/mm^3 *< 25.000 x 10^9/L*
WBC, decreased	2,000 – 2,500/mm^3 *2.000 x 10^9 – 2.500 x 10^9/L*	1,500 – 1,999/mm^3 *1.500 x 10^9 – 1.999 x 10^9/L*	1,000 – 1,499/mm^3 *1.000 x 10^9 – 1.499 x 10^9/L*	< 1,000/mm^3 *< 1.000 x 10^9/L*

LABORATORY					
PARAMETER		**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
CHEMISTRIES	***Standard International Units are listed in italics***				
Acidosis		NA	pH < normal, but ≥ 7.3	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, serum, low		3.0 g/dL – < LLN *30 g/L – < LLN*	2.0 – 2.9 g/dL *20 – 29 g/L*	< 2.0 g/dL *< 20 g/L*	NA
Alkaline Phosphatase		1.25 – 2.5 x ULN†	2.6 – 5.0 x ULN†	5.1 – 10.0 x ULN†	> 10.0 x ULN†
Alkalosis		NA	pH > normal, but ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT (SGPT)		1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
AST (SGOT)		1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10.0 x ULN	> 10.0 x ULN
Bicarbonate, serum, low		16.0 mEq/L – < LLN *16.0 mmol/L – < LLN*	11.0 – 15.9 mEq/L *11.0 – 15.9 mmol/L*	8.0 – 10.9 mEq/L *8.0 – 10.9 mmol/L*	< 8.0 mEq/L *< 8.0 mmol/L*
Bilirubin (Total)					
	Adult and Pediatric >14 days	1.1 – 1.5 x ULN	1.6 – 2.5 x ULN	2.6 – 5.0 x ULN	> 5.0 x ULN
	Infant*†, ≤ 14 days (non-hemolytic)	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	25.1 – 30.0 mg/dL *429 – 513 µmol/L*	> 30.0 mg/dL *> 513.0 µmol/L*
	Infant*†, ≤ 14 days (hemolytic)	NA	NA	20.0 – 25.0 mg/dL *342 – 428 µmol/L*	> 25.0 mg/dL *> 428 µmol/L*
Calcium, serum, high (corrected for albumin)					
	Adult and Pediatric ≥ 7 days	10.6 – 11.5 mg/dL *2.65 – 2.88 mmol/L*	11.6 – 12.5 mg/dL *2.89 – 3.13 mmol/L*	12.6 – 13.5 mg/dL *3.14 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
	Infant*†, < 7 days	11.5 – 12.4 mg/dL *2.88 – 3.10 mmol/L*	12.5 – 12.9 mg/dL *3.11 – 3.23 mmol/L*	13.0 – 13.5 mg/dL *3.245 – 3.38 mmol/L*	> 13.5 mg/dL *> 3.38 mmol/L*
Calcium, serum, low					
	Adult and Pediatric ≥ 7 days	7.8 – 8.4 mg/dL *1.95 – 2.10 mmol/L*	7.0 – 7.7 mg/dL *1.75 – 1.94 mmol/L*	6.1 – 6.9 mg/dL *1.53 – 1.74 mmol/L*	< 6.1 mg/dL *< 1.53 mmol/L*
	Infant*†, < 7 days	6.5 – 7.5 mg/dL *1.63 – 1.88 mmol/L*	6.0 – 6.4 mg/dL *1.50 – 1.62 mmol/L*	5.50 – 5.90 mg/dL *1.38 – 1.51 mmol/L*	< 5.50 mg/dL *< 1.38 mmol/L*
Cardiac troponin I (cTnI)		NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer

LABORATORY					
PARAMETER		**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Cardiac troponin T (cTnT)		NA	NA	NA	≥ 0.20 ng/mL OR Levels consistent with myocardial infarction or unstable angina as defined by the manufacturer
Cholesterol (fasting)					
	Adult ≥ 18 years	200 – 239 mg/dL *5.18 – 6.19 mmol/L*	240 – 300 mg/dL *6.20 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
	Pediatric < 18 years	170 – 199 mg/dL *4.40 – 5.15 mmol/L*	200 – 300 mg/dL *5.16 – 7.77 mmol/L*	> 300 mg/dL *> 7.77 mmol/L*	NA
Creatine Kinase		3.0 – 5.9 x ULN†	6.0 – 9.9 x ULN†	10.0 – 19.9 x ULN†	≥ 20.0 x ULN†
Creatinine		1.1 – 1.3 x ULN†	1.4 – 1.8 x ULN†	1.9 – 3.4 x ULN†	≥ 3.5 x ULN†
Glucose, serum, high					
	Nonfasting	116 – 160 mg/dL *6.44 – 8.88 mmol/L*	161 – 250 mg/dL *8.89 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*
	Fasting	110 – 125 mg/dL *6.11 – 6.94 mmol/L*	126 – 250 mg/dL *6.95 – 13.88 mmol/L*	251 – 500 mg/dL *13.89 – 27.75 mmol/L*	> 500 mg/dL *> 27.75 mmol/L*
Glucose, serum, low					
	Adult and Pediatric ≥ 1 month	55 – 64 mg/dL *3.05 – 3.55 mmol/L*	40 – 54 mg/dL *2.22 – 3.06 mmol/L*	30 – 39 mg/dL *1.67 – 2.23 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*
	Infant*†, < 1 month	50 – 54 mg/dL *2.78 – 3.00 mmol/L*	40 – 49 mg/dL *2.22 – 2.77 mmol/L*	30 – 39 mg/dL *1.67 – 2.21 mmol/L*	< 30 mg/dL *< 1.67 mmol/L*
Lactate		ULN - < 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
LDL cholesterol (fasting)					
	Adult ≥ 18 years	130 – 159 mg/dL *3.37 – 4.12 mmol/L*	160 – 190 mg/dL *4.13 – 4.90 mmol/L*	≥ 190 mg/dL *≥ 4.91 mmol/L*	NA
	Pediatric > 2 - < 18 years	110 – 129 mg/dL *2.85 – 3.34 mmol/L*	130 – 189 mg/dL *3.35 – 4.90 mmol/L*	≥ 190 mg/dL *≥ 4.91 mmol/L*	NA
Lipase		1.1 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 5.0 x ULN	> 5.0 x ULN

LABORATORY					
PARAMETER		**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Magnesium, serum, low		1.2 – 1.4 mEq/L *0.60 – 0.70 mmol/L*	0.9 – 1.1 mEq/L *0.45 – 0.59 mmol/L*	0.6 – 0.8 mEq/L *0.30 – 0.44 mmol/L*	< 0.60 mEq/L *< 0.30 mmol/L*
Pancreatic amylase		1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN
Phosphate, serum, low					
	Adult and Pediatric > 14 years	2.5 mg/dL – < LLN *0.81 mmol/L – < LLN*	2.0 – 2.4 mg/dL *0.65 – 0.80 mmol/L*	1.0 – 1.9 mg/dL *0.32 – 0.64 mmol/L*	< 1.00 mg/dL *< 0.32 mmol/L*
	Pediatric 1 year – 14 years	3.0 – 3.5 mg/dL *0.97 – 1.13 mmol/L*	2.5 – 2.9 mg/dL *0.81 – 0.96 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL *< 0.48 mmol/L*
	Pediatric < 1 year	3.5 – 4.5 mg/dL *1.13 – 1.45 mmol/L*	2.5 – 3.4 mg/dL *0.81 – 1.12 mmol/L*	1.5 – 2.4 mg/dL *0.48 – 0.80 mmol/L*	< 1.50 mg/dL *< 0.48 mmol/L*
Potassium, serum, high		5.6 – 6.0 mEq/L *5.6 – 6.0 mmol/L*	6.1 – 6.5 mEq/L *6.1 – 6.5 mmol/L*	6.6 – 7.0 mEq/L *6.6 – 7.0 mmol/L*	> 7.0 mEq/L *> 7.0 mmol/L*
Potassium, serum, low		3.0 – 3.4 mEq/L *3.0 – 3.4 mmol/L*	2.5 – 2.9 mEq/L *2.5 – 2.9 mmol/L*	2.0 – 2.4 mEq/L *2.0 – 2.4 mmol/L*	< 2.0 mEq/L *< 2.0 mmol/L*
Sodium, serum, high		146 – 150 mEq/L *146 – 150 mmol/L*	151 – 154 mEq/L *151 – 154 mmol/L*	155 – 159 mEq/L *155 – 159 mmol/L*	≥ 160 mEq/L *≥ 160 mmol/L*
Sodium, serum, low		130 – 135 mEq/L *130 – 135 mmol/L*	125 – 129 mEq/L *125 – 129 mmol/L*	121 – 124 mEq/L *121 – 124 mmol/L*	≤ 120 mEq/L *≤ 120 mmol/L*
Triglycerides (fasting)		NA	500 – 750 mg/dL *5.65 – 8.48 mmol/L*	751 – 1,200 mg/dL *8.49 – 13.56 mmol/L*	> 1,200 mg/dL *> 13.56 mmol/L*
Uric acid		7.5 – 10.0 mg/dL *0.45 – 0.59 mmol/L*	10.1 – 12.0 mg/dL *0.60 – 0.71 mmol/L*	12.1 – 15.0 mg/dL *0.72 – 0.89 mmol/L*	> 15.0 mg/dL *> 0.89 mmol/L*
URINALYSIS ***Standard International Units are listed in italics***					
Hematuria (microscopic)		6 – 10 RBC/HPF	> 10 RBC/HPF	Gross, with or without clots OR with RBC casts	Transfusion indicated
Proteinuria, random Collection		1 +	2 – 3 +	4 +	NA

LABORATORY					
PARAMETER		**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
Proteinuria, 24 hour collection					
	Adult and Pediatric ≥ 10 years	200 – 999 mg/24 h *0.200 – 0.999 g/d*	1,000 – 1,999 mg/24 h *1.000 – 1.999 g/d*	2,000 – 3,500 mg/24 h *2.000 – 3.500 g/d*	> 3,500 mg/24 h *> 3.500 g/d*
	Pediatric > 3 mo -< 10 years	201 – 499 mg/m^2/24 h *0.201 – 0.499 g/d*	500 – 799 mg/m^2/24 h *0.500 – 0.799 g/d*	800 – 1,000 mg/m^2/24 h *0.800 – 1.000 g/d*	> 1,000 mg/ m^2/24 h *> 1.000 g/d*

* Values are for term infants. Preterm infants should be assessed using local normal ranges.
† Use age and sex appropriate values (e.g., bilirubin).

Reference

Division of AIDS, Regulatory Support Center. Manual for grading the severity of adult and pediatric adverse events. Version 1.0 - December 2004 (Clarification dated August 2009) Bethesda, MD: DAIDS/RCC, 2009. Available at: http://rsc.tech-res.com/safetyandpharmacovigilance/ (accessed 21 March, 2014)

11.4. Appendix 4: Liver Safety Drug Restart or Rechallenge Guidelines

VSLC GUIDELINES FOR DRUG RESTART OR RECHALLENGE AFTER STOP FOR LIVER CRITERIA

1. **Drug rechallenge** may be considered for a subject exhibiting compelling benefit for a critical medicine following drug-induced liver injury, if favourable benefit: risk and no alternative medicine available (Table 8, Figure 3)
2. 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 HLA marker of liver injury, when liver chemistries improve to within 1.5x baseline and ALT<3xULN) (Table 9, Figure 4).

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

Risk factors for a fatal drug rechallenge outcome include:

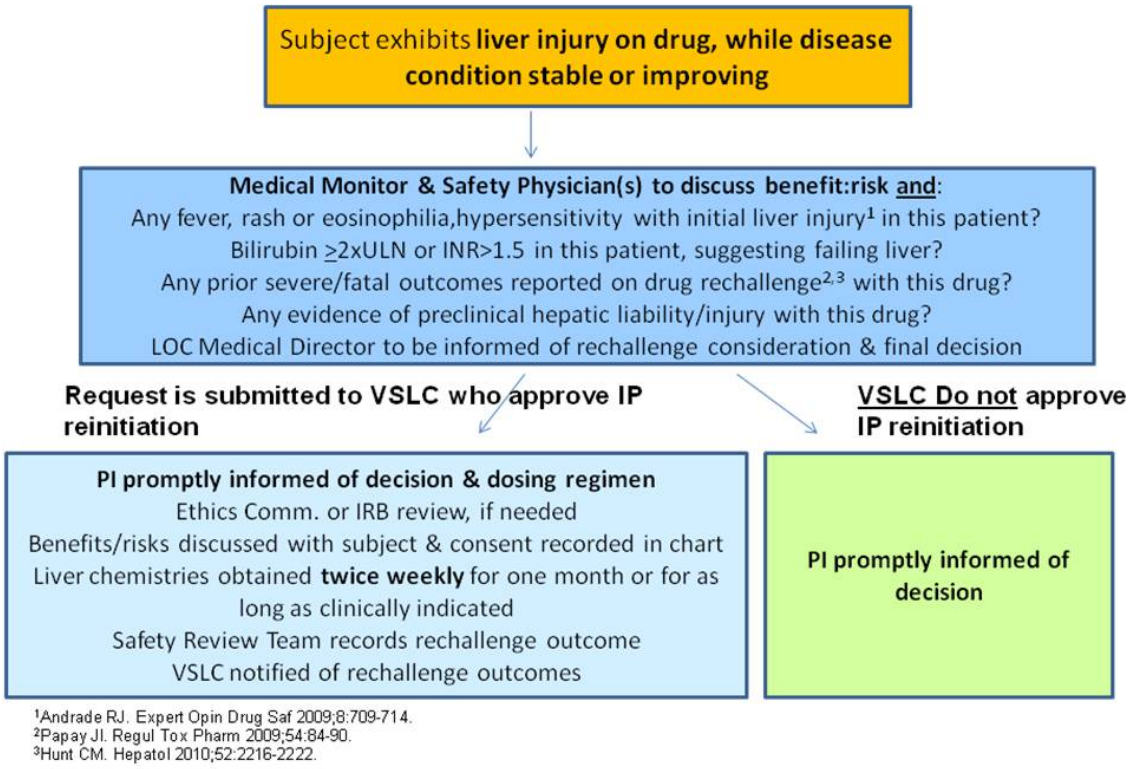
- hypersensitivity with initial liver injury (e.g. fever, rash, eosinophilia) [Andrade, 2009]
- jaundice or bilirubin≥2xULN with initial liver injury
- prior serious adverse event or fatality has earlier been observed with drug rechallenge [Papay, 2009; Hunt, 2010]
- evidence of drug-related preclinical liability (e.g. reactive metabolites; mitochondrial impairment [Hunt, 2010])

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

- Principal Investigator (PI) requests consideration of drug rechallenge for a subject receiving ***compelling benefit from a critical or life-saving drug***, who exhibits liver chemistry elevation meeting subject stopping criteria, with no alternative treatment
- By definition treatment naïve subjects will only be considered for rechallenge if they were infected with a multi-resistant virus.
- Medical Monitor and Global Clinical Safety and Pharmacovigilance (GCSP) Physician to review the subject's rechallenge risk factors (consultation with the Hepatotoxicity Panel is available) and ***complete checklist*** **(**Table 8**).**

- The Medical Monitor and GCSP Physician ***are accountable to review and agree on:***
  - ***compelling*** benefit of the investigational product (IP) ***for this subject and no alternative therapy***
  - ***must present source data defining the patient's current resistance profile with documented evidence of extensive drug resistance and previous drug history***
  - Relative benefit-risk of drug rechallenge, with consideration of the following high risk factors:
    - Initial liver injury event included: fever, rash, eosinophilia, or bilirubin≥2xULN (or direct bilirubin >35% of total, if available)
    - subject currently exhibits severe liver injury defined by: ALT ≥3xULN, ≥bilirubin ≥2xULN (direct bilirubin >35% of total, if available), or INR1.5
    - SAE or fatality has earlier been observed with IP rechallenge
    - IP associated with known preclinical hepatic liability/ injury
- Relevant physicians must review and agree on request for drug rechallenge:
  - Safety Team Leader, VP, or Senior Safety Physician
  - Medicines Development Leader and Project Physician Leader.
  - Request is taken to full VSLC for final decision.

Figure 3 VSLC process for drug rechallenge approval or disapproval



[1]Andrade RJ. Expert Opin Drug Saf 2009;8:709-714.
[2]Papay JI. Regul Tox Pharm 2009;54:84-90.
[3]Hunt CM. Hepatol 2010;52:2216-2222.

The local operating company (LOC) medical director (ViiV and GSK where applicable) should be informed that study drug rechallenge is under consideration and of the final decision, whether or not to proceed.

Table 8 Checklist for drug rechallenge for critical medicine (Following drug-induced liver injury, drug rechallenge is associated with 13% mortality across all drugs in prospective studies)

	Yes	No
Compelling benefit of the investigational product (IP) **for this subject and no alternative therapy**. **Provide brief explanation**:		
Relative benefit-risk favorable for drug rechallenge, after considering the **following high risk factors**:		
• Initial liver injury event included:		
○ fever, rash, eosinophilia, or hypersensitivity		
○ or bilirubin≥2xULN (direct bilirubin >35% of total)		
○ Subject currently exhibits ALT ≥3xULN, bilirubin ≥2xULN (direct bilirubin >35% of total, if available), or INR≥1.5		
○ SAE or fatality has earlier been observed with IP rechallenge **If yes, please provide brief explanation**:		
○ IP associated with known preclinical hepatic liability/ injury		
○ Source data defining the patients current resistance profile		
○ Previous drug history		

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 IP, 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 9).
  - ***must present source data defining the patient's current resistance profile with documented evidence of extensive drug resistance and previous drug history***.
- The LOC medical director (ViiV 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 9 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.

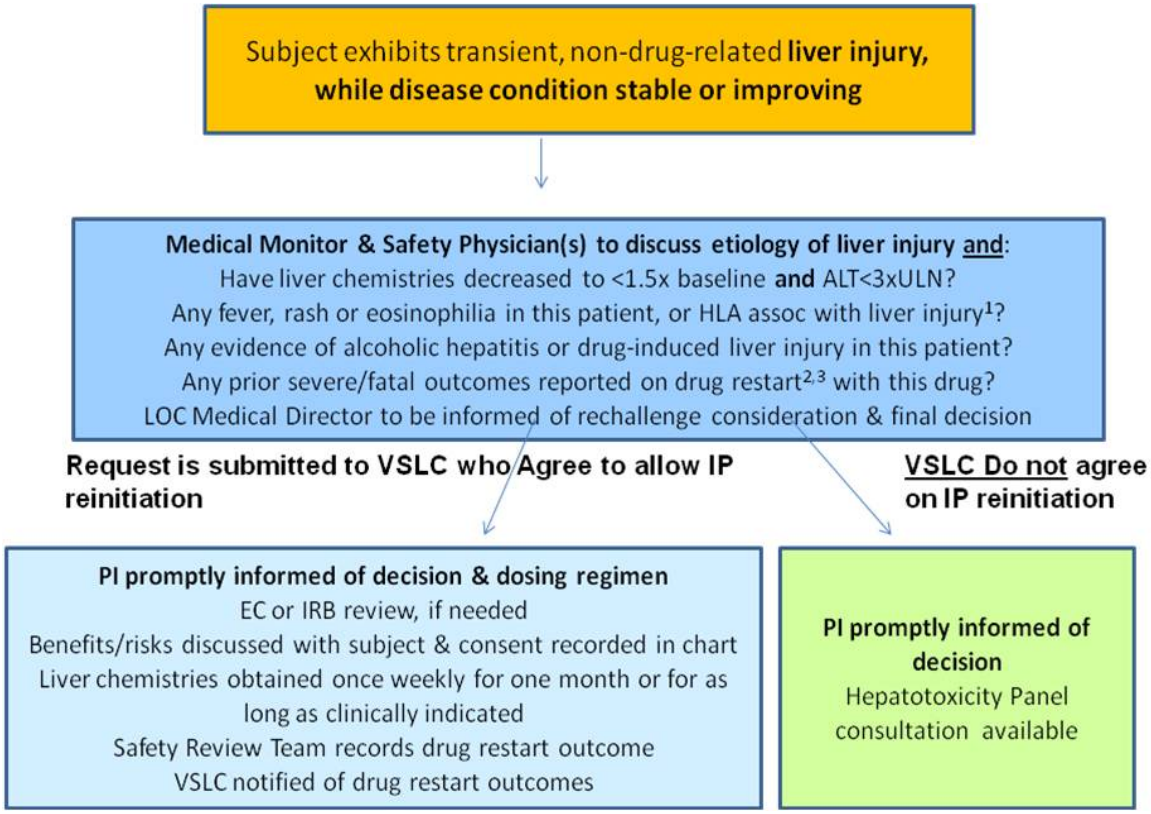
	Yes	No
Is subject stable or improving on the investigational product (IP)?		
Do not restart if the **following risk factors at initial liver injury**:		
• fever, rash, eosinophilia, or hypersensitivity		
• drug-induced liver injury		
• alcoholic hepatitis (AST>ALT, typically <10xULN)		
• IP has an HLA genetic marker associated with liver injury (e.g. lapatinib, abacavir, amoxicillin/clavulanate)		
Source data defining the patients current resistance profile		
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 or Rechallenge following VSLC decision

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

- Medical Monitor must notify PI of VSLC's rechallenge (or restart) decision and recommended dosing regimen in writing and Medical Monitor must record note in study files.
- The Safety Review Team must record rechallenge (or restart) outcomes and the GCSP Physician must send these to the VSLC

- All severe reactions (rechallenge associated with bilirubin>2xULN or jaundice, or INR≥1.5), SAEs or fatalities with drug rechallenge (or 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 rechallenge or 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.
  - ***Targeted drug rechallenge or drug restart consent form must be used.***
- 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 ***twice weekly for 'rechallenge' cases*** and ***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, IP should be discontinued as protocol specified.

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

Rechallenge/restart safety outcomes:

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

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.

11.5. Appendix 5: Pharmacogenetic Research

Pharmacogenetics – Background

Pharmacogenetics (PGx) is the study of variability in drug response due to hereditary factors in populations. There is increasing evidence that an individual's genetic background (i.e. genotype) may impact the pharmacokinetics (absorption, distribution, metabolism, elimination), pharmacodynamics (relationship between concentrations and pharmacologic effects or the time course of pharmacologic effects) and/or clinical outcome (in terms of efficacy and/or safety and tolerability). Some reported examples of PGx associations with safety/adverse events include:

Drug	Disease	Gene Variant	Outcome
Abacavir	HIV [Hetherington, 2002; Mallal, 2002; Mallal, 2008]	*HLA-B* 57:01 (Human Leukocyte Antigen B)*	Carriage of the *HLA-B*57:01* variant has been shown to increase a patient's risk for experiencing hypersensitivity to abacavir. Prospective *HLA-B*57:01* screening and exclusion of *HLA-B*57:01* positive patients from abacavir treatment significantly decreased the incidence of abacavir hypersensitivity. Treatment guidelines and abacavir product labeling in the United States and Europe now recommend (US) or require (EU) prospective *HLA-B*57:01* screening prior to initiation of abacavir to reduce the incidence of abacavir hypersensitivity. *HLA-B*57:01* screening should supplement but must never replace clinical risk management strategies for abacavir hypersensitivity.
Carbamazepine	Seizure, Bipolar disorders & Analgesia [Chung, 2010; Ferrell, 2008]	*HLA-B*15:02*	Independent studies indicated that patients of East Asian ancestry who carry *HLA-B*15:02* are at higher risk of Stevens-Johnson Syndrome and toxic epidermal necrolysis. Regulators, including the US FDA and the Taiwanese TFDA, have updated the carbamazepine drug label to indicate that patients with ancestry in genetically at risk populations should be screened for the presence of *HLA-B*15:02* prior to initiating treatment with carbamazepine.
Irinotecan	Cancer [Innocenti, 2004; Liu, 2008; Schulz, 2009]	*UGT1A1*28*	Variations in the *UGT1A1* gene can influence a patient's ability to break down irinotecan, which can lead to increased blood levels of the drug and a higher risk of side effects. A dose of irinotecan that is safe for one patient with a particular *UGT1A1* gene variation might be too high for another patient without this variation, raising the risk of certain side-effects that include neutropenia following initiation of Irinotecan treatment. The irinotecan drug label indicates that individuals who have two copies of the *UGT1A1*28* variant are at increased risk of neutropenia. A genetic blood test is available that can detect variations in the gene.

A key component to successful PGx research is the collection of samples during the conduct of clinical studies.

Collection of whole blood samples, even when no *a priori* hypothesis has been identified, may enable PGx analysis to be conducted if at any time it appears that there is a potential unexpected or unexplained variation in response to DTG or any of the HIV medicines included in this study.

Pharmacogenetic Research Objectives

The objective of the PGx research (if there is a potential unexpected or unexplained variation) is to investigate a relationship between genetic factors and response to DTG or any of the HIV medicines included in this study. If at any time it appears there is potential variability in response in this clinical study or in a series of clinical studies with DTG, the following objectives may be investigated – the relationship between genetic variants and study treatment with respect to:

- Relationship between genetic variants and the pharmacokinetics and/or pharmacodynamics of DTG or other HIV medicines used in this study;
- Relationship between genetic variants and safety and/or tolerability of DTG or other HIV medicines used in this study;
- Relationship between genetic variants and efficacy of DTG or other HIV medicines used in this study.

Study Population

Any subject who is enrolled in the clinical study, can participate in PGx research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the PGx research.

Subject participation in the PGx research is voluntary and refusal to participate will not indicate withdrawal from the clinical study or result in any penalty or loss of benefits to which the subject would otherwise be entitled.

Study Assessments and Procedures

Blood samples can be taken for Deoxyribonucleic acid (DNA) extraction and used in PGx assessments.

In addition to any blood samples taken for the clinical study, a whole blood sample (6 mL) will be collected for the PGx research using a tube containing EDTA. It is recommended that the blood sample be taken at the first opportunity after a subject has been randomised and provided informed consent for PGx research, but may be taken at any time while the subject is participating in the clinical study.

- The PGx sample is labelled (or "coded") with a study specific number that can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number). The blood sample is taken on a single occasion unless a duplicate sample is required due to inability to utilise the original sample.

The DNA extracted from the blood sample may be subjected to sample quality control analysis. This analysis will involve the genotyping of several genetic markers to confirm the integrity of individual samples. If inconsistencies are noted in the analysis, then those samples may be destroyed.

The need to conduct PGx analysis may be identified after a study (or a set of studies) of DTG (or any of the HIV medicines included in this study) has been completed and the clinical study data reviewed. In some cases, the samples may not be studied. e.g., no questions are raised about how people respond to DTG (or any of the HIV medicines included in this study).

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will use samples collected from the study for the purpose stated in this protocol and in the informed consent form.

Subjects can request their sample to be destroyed at any time.

Subject Withdrawal from Study

If a subject who has consented to participate in PGx research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the PGx sample, if already collected:

- Continue to participate in the PGx research with the PGx sample retained for analysis
- Withdraw from the PGx research and destroy the PGx sample

If a subject withdraws consent for PGx research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records. The investigator should forward the Pharmacogenetic Sample Destruction Request Form to GSK as directed on the form. This can be done at any time when a subject wishes to withdraw from the PGx research or have their sample destroyed whether during the study or during the retention period following close of the main study.

Screen and Baseline Failures

If a blood sample for PGx research has been collected and it is determined that the subject does not meet the entry criteria for participation in the clinical study, then the investigator should instruct the participant that their PGx sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Pharmacogenetics Analyses

1. Specific genes may be studied that encode the drug targets, or drug mechanism of action pathways, drug metabolizing enzymes, drug transporters or which may underpin adverse events, disease risk or drug response. These candidate genes may include a common set of ADME (Absorption, Distribution, Metabolism and Excretion) genes that are studied to determine the relationship between gene variants or treatment response and/or tolerance.

In addition, continuing research may identify other enzymes, transporters, proteins or receptors that may be involved in response to DTG or any of the HIV medicines included in this study. The genes that may code for these proteins may also be studied.

2. Genome-wide scans involving a large number of polymorphic markers (e.g., single nucleotide polymorphisms) at defined locations in the genome, often correlated with a candidate gene, may be studied to determine the relationship between genetic variants and treatment response or tolerance. This approach is often employed when a definitive candidate gene(s) does not exist and/or the potential genetic effects are not well understood.

If applicable and PGx research is conducted, appropriate statistical analysis methods will be used to evaluate pharmacogenetic data in the context of the other clinical data. Results of PGx investigations will be reported either as part of the main clinical study report or as a separate report. Endpoints of interest from all comparisons will be descriptively and/or graphically summarised as appropriate to the data. A detailed description of the analysis to be performed will be documented in the study reporting and analysis plan (RAP) or in a separate pharmacogenetics RAP, as appropriate.

Informed Consent

Subjects who do not wish to participate in the PGx research may still participate in the clinical study. PGx informed consent must be obtained prior to any blood being taken for PGx research.

Provision of Study Results and Confidentiality of Subject's PGx Data

GSK may summarise the PGx research results in the clinical study report, or separately, or may publish the results in scientific journals.

GSK does not inform the investigator, subject, or anyone else (e.g., family members, study investigators, primary care physicians, insurers, or employers) of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from PGx studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined.

References

Chung WH, Hung SL, Chen YT. Genetic predisposition of life-threatening antiepileptic-induced skin reactions. Expert Opin Drug Saf. 2010; 9: 15-21.

Ferrell PB, McLeod HL. Carbamazepine, HLA-B*1502 and risk of Stevens-Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations. Pharmacogenomics. 2008; 9: 1543-1546.

Hetherington S, Hughes AR, Mosteller M, Shortino D, Baker KL, Spreen W, Lai E, Davies K, Handley A, Dow DJ, Fling ME, Stocum M, Bowman C, Thurmond LM, Roses AD. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. Lancet. 2002; 359:1121-1122.

Innocenti F, Undevia SD, Iyer L, Chen PX, Das S, Kocherginsky M, Karrison T, Janisch L, Ramirez J, Rudin CM, Vokes EE, Ratain MJ. Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. J Clin Oncol 2004; 22: 1382-1388.

Liu CY, Chen PM, Chiou TJ, Liu JH, Lin JK, Lin TC, Chen WS, Jiang JK, Wang HS, Wang WS. UGT1A1*28 polymorphism predicts irinotecan-induced severe toxicities without affecting treatment outcome and survival in patients with metastatic colorectal carcinoma. Cancer. 2008; 112: 1932-1940.

Mallal S, Nolan D, Witt C, Masel G, Martin AM, Moore C, Sayer D, Castley A, Mamotte C, Maxwell D, James I. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. Lancet. 2002; 359:727-732.

Mallal S, Phillips E, Carosi G, Molina JM, Workman C, Tomazic J, Jägel-Guedes E, Rugina S, Kozyrev O, Cid JF, Hay P, Nolan D, Hughes S, Hughes A, Ryan S, Fitch N, Thorborn D, Benbow A; PREDICT-1 Study Team. HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med. 2008; 358; 568-579

Schulz C, Heinemann V, Schalhorn A, Moosmann N, Zwingers T, Boeck S, Giessen C, Stemmler HJ. UGT1A1 gene polymorphism: Impact on toxicity and efficacy of irinotecan-based regimens in metastatic colorectal cancer. World J. Gastroenterol. 2009; 15: 5058-5066.

11.6. Appendix 6: Country Specific Requirements

No country-specific requirements exist.

11.7. Appendix 7: Protocol Changes

11.7.1. Protocol Amendment 01

This protocol amendment applies to all participating sites.

Rationale for Protocol Amendment 01:

i. Medical Monitor Contact Information and Serious Adverse Events (SAE) Contact Information has been updated with a secondary contact.

ii. Removal of exclusion criterion 18 which prohibits enrolment of subject with creatinine clearance of <50 mL/min via the CKD-EPI method. This exclusion criterion was included in error. Both DTG and LPV/RTV can be administered in patients with renal impairment, and no dosage adjustments are required.

iii. Reference to allergic reaction criteria in Section 4.5 "Withdrawal Criteria" which was omitted in the original protocol. As per Section 6.4.4.6, subjects with Grade ≥3 allergic reactions that are considered to be possibly or probably related to the IP should permanently discontinue the IP regimen and the subject should be withdrawn from the study.

iv. The HIV treatment satisfaction questionnaire status version (HIVTSQs) and HIVTSQ change version (HIVTSQc) will be administered at different times following feedback of the developer of these questionnaires. The HIVTSQs will be administered at Baseline (Day 1), Week 4, Week 24, Week 48 and withdrawal while the HIVTSQc will be administered at Week 48 and at withdrawal (in addition to the HIVTSQs) rather than at Week 24. The HIVTSQs-14 item measure, which includes the 10 items in the standard HIVTSQs but has four additional items for testing, will be used in the study.

v. In Section 6.4.4.5 "Decline in renal function", estimated GFR (by the CKD-EPI method) is referred to instead of CrCl in order to clarify what formula should be used to evaluate renal function.

vi. Updates to reference [Kaletra EU Summary of Product Characteristics; Kaletra US Product Information].

A list of specific changes is provided below. Unless stated otherwise, new text is represented in bold font, and deleted text in strikethrough font.

SPONSOR INFORMATION PAGE

~~Sponsor~~ Medical Monitor Contact Information **and Serious Adverse Events (SAE) Contact Information**:

PPD MD
GlaxoSmithKline
Research Triangle Park

Five Moore Drive, Research Triangle Park, NC (USA)
Telephone: +PPD
Mobile: +PPD
PPD

Secondary contact:

PPD **MD**
GlaxoSmithKline
Collegeville, PA (USA)
Telephone: +PPD
Mobile: +PPD
PPD

~~**Sponsor Serious Adverse Events (SAE) Contact Information:**~~

PPD
~~Research Triangle Park~~
~~Five Moore Drive, Research Triangle Park, NC (USA)~~
~~Telephone: +~~PPD
~~Mobile: +~~PPD
PPD

4.3. Exclusion Criteria

The following text has been deleted:

~~18. Subject has creatinine clearance of <50 mL/min via the CKD-EPI method.~~

4.5 Withdrawal Criteria

Subjects **must** be discontinued from the study for any of the following reasons:...

- **Allergic reaction or** rash criteria as described in **Section 6.4.4.6 and** Section 6.4.4.7 **respectively,** are met and no compelling alternate cause is identified;

6.1. Time and Events Schedule

Table 1 Time and Events Table

In addition to Baseline (Day 1), Week 4, Week 48 and at withdrawal, the HIVTSQs will also be administered at Week 24. The HIVTSQc will be administered at Week 48 and also at withdrawal rather than at Week 24.

Samples for quantitative plasma HIV-1 RNA PCR and lymphocyte subset and plasma for storage will not be collected at Follow-up.

Footnote b. has been amended: For subjects who completed randomised DTG through Week 52 and entered into the DTG Continuation Phase: subjects completing the DTG Continuation Phase must return to the clinic when transitioning to commercial supplies. Conduct study assessments**, with the exception of dispensing IP,** as specified **for all**

Continuation Phase visits ~~per the follow-up visit schedule~~ at this end of Continuation Phase visit.

6.4.4.5 Decline in renal function

Subjects who experience an increase in creatinine from Baseline of 45 µMol/L (or 0.5 mg/dL) should return for a confirmatory assessment within 2 to 4 weeks. A urinalysis and urine albumin/creatinine and urine total protein/albumin ratios should 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 have a decline in ~~CrCl~~ **the estimated GFR (using the CKD-EPI method)** of >50% must return for a confirmatory assessment as soon as possible. A urinalysis and urine albumin/creatinine and urine protein/creatinine ratios should be done at this confirmatory visit. If the estimated ~~CrCl~~ **GFR** has declined by >50% (confirmed), then IP should be withheld and the investigator should contact the study medical monitor to discuss the rationale for restarting study drugs (if appropriate). Consideration for confounding factors (e.g. background therapy, other medications, dehydration, concurrent conditions) should be taken into account, and a nephrology consult may be obtained. If a subject is also receiving TDF, then a switch to an alternative nucleoside should be considered if restarting IP. One background NRTI change is allowed for management of drug toxicity as described in Section 6.4.4, "Specific Toxicities/Adverse Event Management". If IP is reinitiated, it should have been withheld for no more than 4 weeks. If IP is not reinitiated the subject must be withdrawn.

8.3.5.3. Health outcomes analyses

HIVTSQ

The HIVTSQ was developed to evaluate treatments for HIV and patient satisfaction [Woodcock, 2001; Woodcock, 2006]. The higher the score, the greater the improvement in treatment satisfaction as compared to the past few weeks. A smaller score represents a decline in treatment satisfaction compared to the past few weeks.

This study will use the **14-item** HIVTSQ~~(s)~~ (status version) and the ~~revised~~**14-item** HIVTSQ~~(c)~~ (change version)**, both including the 10 items of the standard HIVTSQ but having four additional items for testing**. These measures will assess change in treatment satisfaction over time (in the same subjects) and compare current satisfaction with previous treatment satisfaction, from an earlier time point.

10. REFERENCES

The following references have been updated.

Kaletra EU Summary of Product Characteristics, **February 2014**~~May2013~~.

Kaletra US Product Information, **November**~~January~~ 2013.

11.7.2. Protocol Amendment 02

Protocol changes for Amendment 02, from protocol changes to Amendment 01 (30-Apr-2014)

This protocol amendment applies to all participating sites.

Amendment 02 Summary and Rationale:

i. The author list has been updated.

ii. Sponsor, Medical Monitor and Serious Adverse Events (SAE) Contact Information has been updated.

iii. Following an IDMC recommendation to discontinue the LPV/RTV arm and switch subjects currently receiving LPV/RTV in the study to a regimen with DTG, changes to the study design have been made accordingly. Additional sensitivity analyses are planned for the primary endpoint as a consequence of these changes.

iv. The section on Suicidality monitoring has been updated with further guidance following inclusion of additional adverse drug reactions in the DTG investigator's brochure: depression, suicidal ideation or suicide attempt (particularly in patients with a pre-existing history of depression or psychiatric illness).

v. Updates to the Time & Events Table (Section 6.1) and the Health Outcomes Analyses section to provide clearer guidance on when health outcomes assessments will be conducted in the case of early withdrawal from the study and on MMAS-8 and GSRS scores, respectively.

vi. Updates to references: Kaletra EU Summary of Product Characteristics, Kaletra US Product Information, WHO treatment guidelines, Investigator's Brochure.

A list of specific changes is provided below. Unless stated otherwise, new text is represented in bold font, and deleted text in strikethrough font.

List of Specific Changes

TITLE PAGE

Author(s): PPD
PPD

SPONSOR INFORMATION PAGE

This study is sponsored by ViiV Healthcare. ~~GlaxoSmithKline is implementing and managing all aspects of this study.~~**GlaxoSmithKline is supporting ViiV Healthcare in the conduct of this study.**

Sponsor Name and Legal Registered Address (excluding US)~~Sponsor Legal Registered Address~~:

ViiV Healthcare **UK Limited**
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK
~~Telephone: +44 (0)20 8380 6200~~

US IND Sponsor Name and Legal Registered Address~~Sponsor Contact Address~~:

ViiV Healthcare **Company**
Five Moore Drive
P.O. 13398
Research Triangle Park, NC 27709-3398, USA
Telephone: + 1 919 483 2100

~~In some countries, the clinical trial sponsor may be the local ViiV Healthcare affiliate company (or designee). Where applicable, the details of the Sponsor and contact person will be provided to the relevant regulatory authority as part of the clinical trial submission.~~ **In some countries, local law requires that the Clinical Trial sponsor is a local company legal entity. In these instances, the appropriate company to be identified as sponsor must be agreed with the global ViiV Healthcare clinical team and signed off by the VP and Head, Global Research and Medical Strategy.**

Medical Monitor Contact Information and Serious Adverse Events (SAE) Contact Information:

PPD **MD, PhD**
ViiV Healthcare
980 Great West Road
Brentford, Middlesex
TW8 9GS
UK
Mobile: +PPD
PPD
PPD
~~GlaxoSmithKline~~
~~Research Triangle Park~~
~~Five Moore Drive, Research Triangle Park, NC (USA)~~
~~Telephone: +~~PPD
~~Mobile: +~~PPD
PPD

Secondary contact:

PPD **MD**
ViiV Healthcare

5 Moore Drive
Research Triangle Park, NC 27709
USA
Mobile: +PPD
PPD

PPD ~~, MD~~
~~GlaxoSmithKline~~
~~Collegeville, PA (USA)~~
~~Telephone: +~~PPD
~~Mobile: +~~PPD
PPD

PROTOCOL SUMMARY

Study Design

The following text has been added:

The IDMC completed two of the three pre-planned analyses. Prior to interim analysis #3, the IDMC conducted an ad-hoc review of trial data and observed significant, clinically relevant differences between treatment arms in favour of DTG. The IDMC recommended to the sponsor that the LPV/RTV treatment arm be discontinued and subjects currently receiving LPV/RTV in the study be switched to a regimen with DTG as the third drug, if considered appropriate by the Investigator. As per Protocol Amendment No. 2, subjects randomised to the LPV/RTV arm will either (i) continue receiving LPV/RTV and complete the study after the 4-week treatment extension (see above), or (ii) switch to the DTG arm prior to study completion at Week 52 and continue to have access to DTG in the Continuation Phase until DTG is either locally approved and commercial supplies are available to patients (e.g. through public health services), the patient no longer derives clinical benefit, or the patient meets a protocol-defined reason for discontinuation. Subjects originally randomised to DTG and receiving DTG in the Randomised Phase or in the Continuation Phase are not affected by this IDMC recommendation and Protocol Amendment No. 2.

1.3.1. Risk Assessment

Risk Assessment Table, Psychiatric disorders

Psychiatric disorders including suicide ideation and behaviours are common in HIV-infected patients. The psychiatric profile for DTG (including suicidality, depression, bipolar and hypomania, anxiety and abnormal dreams) was similar **to RAL-** or favourable compared with **EFV-based regimens** ~~other ART~~.

3.1. Study Design

An IDMC **has been** ~~will be~~ instituted to perform periodic reviews of the accumulating data to ensure that subjects are not being sub-optimally treated ~~(see Section 8.3.4.2)~~. **The IDMC completed the first two of the three pre-planned analyses (see Section 8.3.4.2). Prior to the third interim analysis, the IDMC conducted an ad hoc review of trial data and the IDMC observed significant, clinically relevant differences between treatment arms in favour of DTG. The IDMC recommended to the sponsor that the LPV/RTV treatment arm be discontinued and subjects currently receiving LPV/RTV in the study be switched to a regimen with DTG as the third drug, if considered appropriate by the Investigator.**

Randomised Phase: Day 1 to Week 48 + 4-week treatment extension

Following the IDMC's recommendation and as per Protocol Amendment No. 2, subjects randomised to the LPV/RTV arm will either (i) continue receiving LPV/RTV and complete the study after the 4-week treatment extension at Week 52, or (ii) switch to the DTG arm prior to study completion at Week 52 and continue to have access to DTG in the Continuation Phase.

The primary efficacy endpoint corresponds to viral load measurements collected within a ± 6 week window around the Week 48 visit (including data from the Week 52 visit), as per the FDA's Snapshot algorithm, and for this reason, the primary analysis is denoted as occurring at Week 48 with the understanding that data from the Week 52 visit may be included.

DTG Continuation Phase

Subjects randomised to receive DTG who successfully complete 52 weeks of treatment **and subjects originally randomised to receive LPV/RTV but switched to DTG prior to Week 52 (as per Protocol Amendment No. 2)** will continue to have access to DTG (Continuation Phase) until it is either locally approved and commercial supplies are available to patients (e.g. through public health services), the patient no longer derives clinical benefit, or the patient meets a protocol-defined reason for discontinuation. Investigative sites must make arrangements for provision of background NRTIs to all subjects to ensure continued access to these medications during the DTG Continuation Phase (unless provision by the sponsor is mandated by local regulation).

Subjects randomised to the LPV/RTV arm will receive LPV/RTV + two NRTIs through their Week 52 visit only, after which subjects will complete the study and will need to have alternate arrangements in place to access antiretroviral medication (unless mandated by local regulation). **Subjects randomised to the LPV/RTV arm, who switch to the DTG arm prior to study completion at Week 52, will continue to have access to DTG (Continuation Phase) as mentioned above.**

Study Completion

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

- Randomised to LPV/RTV + two NRTIs and completed the Randomised Phase including the Week 52 study visit;
- **Randomised to LPV/RTV + two NRTIs, switched to DTG + two NRTIs and completed the Randomised Phase including the Week 52 study visit, and did not enter the Continuation Phase;**
- **Randomised to LPV/RTV+ two NRTIs, switched to DTG + two NRTIs and completed the Randomised Phase, including the Week 52 study visit, entered and completed the Continuation Phase (defined as remaining on study until commercial supplies of DTG become locally available to patients [e.g. through public health services]).**
- Randomised to DTG + two NRTIs, completed the Randomised Phase including the Week 52 study visit, and did not enter the Continuation Phase;
- Randomised to DTG + two NRTIs, completed the Randomised Phase, including the Week 52 study visit, entered and completed the Continuation Phase (defined as remaining on study until commercial supplies of DTG become locally available to patients [e.g. through public health services]).

Figure 1 Study Schematic

The figure was updated to indicate that a switch from LPV/RTV arm to DTG arm may occur prior to study completion at Week 52, based on Investigator judgement.

4.5. Withdrawal Criteria

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

- Confirmed virologic withdrawal criteria as described in Section 4.6.1 are met;
- Subject requires substitution or dose modification of DTG, or substitution of LPV/RTV (a switch from LPV/RTV 800/200 mg once daily to 400/100 mg twice daily or the opposite switch is allowed**; as per Protocol Amendment No. 2, a switch from LPV/RTV to DTG will also be allowed**);

…

4.6. Virologic Criteria for Subject Management and Viral Resistance Testing

Following Day 1, no changes, or intensification of ART will be permitted prior to meeting confirmed virologic withdrawal criteria or Week 52, with the exception of a

switch from LPV/RTV 800/200 mg once daily to 400/100 mg twice daily or the opposite switch, **a switch from LPV/RTV to DTG as per Protocol Amendment No. 2,** and one allowed background NRTI change for management of drug toxicity as described in Section 6.4.4., "Specific Toxicities/Adverse Event Management". Any NRTI change must ensure a fully active NRTI is still present based on Screening resistance testing. A switch from 3TC to FTC (or vice versa) will not be considered a background NRTI change and is permitted. Subjects unable to manage drug toxicity or tolerate IP (DTG or LPV/RTV) must be discontinued from the study as described in Section 6.4.

5.1.5. Protocol-Permitted Substitutions

A switch of DTG or LPV/RTV is not allowed except for a switch from LPV/RTV 800/200 mg once daily to LPV/RTV 400/100 mg twice daily or the opposite switch. **As per Protocol Amendment No. 2, a switch from LPV/RTV to DTG will be allowed.**

5.3. Blinding

As this is an open-label study, blinding is not required. No summaries of the study data according to actual randomised treatment groups will be available to sponsor staff prior to the planned Week 24 interim analysis. **According to the IDMC Charter, ViiV Healthcare/GSK personnel having direct responsibility for the conduct of the study and its analysis may however review summaries of data by treatment group if the IDMC recommends to the sponsor the termination of a treatment arm or the entire study.**

5.6.4. Prohibited medications for subjects randomised to LPV/RTV

Avanafil added to list of prohibited medications for subjects randomised to LPV/RTV.

5.8. Treatment after the End of the Study

The following text has been added:

Subjects originally randomised to receive LPV/RTV but switched to the DTG arm prior to Week 52 (as per Protocol Amendment No. 2) will continue to have access to DTG (Continuation Phase) until it is either locally approved and commercial supplies are available to patients (e.g. through public health services), the patient no longer derives clinical benefit, or the patient meets a protocol-defined reason for discontinuation. Investigative sites must make arrangements for provision of background NRTIs to all subjects to ensure continued access to these medications

during the DTG Continuation Phase (unless provision by the sponsor is mandated by local regulation).

6.1. Time and Events Schedule

The following footnote has been added:

j. Health outcomes assessments will only be conducted at Withdrawal if the Withdrawal visit occurs at or prior to Week 48.

6.4.10. Suicidality Monitoring

Patients with HIV infection may occasionally present with symptoms of depression and/or suicidality (suicidal ideation or behaviour). **In addition, there have been some reports of depression, suicidal ideation and behaviour (particularly in patients with a pre-existing history of depression or psychiatric illness) in some patients being treated with 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 behaviour or any other unusual changes in behaviour. It is recommended that the Investigator consider mental health consultation or referral for subjects who experience signs of suicidal ideation or behaviour. **Subjects presenting with new onset/treatment-emergent depression should be advised to contact the investigator immediately if symptoms of severe acute depression (including suicidal ideation/attempts) develop, because medical intervention and discontinuation of the study medication may be required.**

6.6.2. HIV-1 Pol Viral Genotyping and Phenotyping

Subjects meeting a 'confirmed virologic withdrawal criterion' (see Section 4.6.3) will have plasma samples tested for HIV-1 PRO and RT genotype and phenotype and HIV-1 integrase genotype and phenotype from both Baseline samples and from samples collected at the time of meeting a 'suspected virologic withdrawal criterion'; these results will be reported to the Investigator as soon as available to provide guidance for election of an alternative regimen.

HIV-1 PRO and RT genotype and phenotype ~~and HIV-1 integrase genotype and phenotype~~ will also be determined on the Baseline isolates from all subjects, if possible. When samples cannot be analysed by Monogram Biosciences, Baseline isolate resistance testing may be performed at location(s) to be described in the SPM.

8.3.4.2. IDMC interim analyses

An IDMC ~~will be~~ **has been** instituted to provide independent review of the accumulating data, primarily to ensure subjects are not being sub-optimally treated in either arm.

Three formal interim analyses ~~are~~ **were** planned for review by the IDMC (Table 5).

…

The IDMC completed interim analyses #1 and #2. Prior to interim analysis #3, the IDMC conducted an ad hoc review of trial data and observed significant, clinically relevant differences between treatment arms in favour of DTG. The IDMC recommended to the sponsor that the LPV/RTV treatment arm be discontinued and subjects currently receiving LPV/RTV in the study be switched to a regimen with DTG as the third drug, if considered appropriate by the Investigator. Interim analysis #3 will no longer take place.

8.3.5.1. Efficacy analyses

The following text has been added:

Following the IDMC recommendation to switch LPV/RTV subjects to DTG, additional sensitivity analyses will be conducted for the primary endpoint. Further details of these analyses and any other impacted analyses will be included in the RAP.

8.3.5.3. Health outcomes analyses

MMAS-8

The original Morisky Medication Adherence Scale (MMAS) was a four item scale that was developed to assess medication adherence with chronic conditions, such as antihypertensive agents [Morisky, 1986]. More recently, an eight-item self-reported scale was developed called the Morisky 8-Item Medication Adherence Scale (MMAS-8) [Morisky, 2008]. Scores of 8 indicate CCI [redacted], and scores of **less than** 6 ~~or less~~ indicate CCI [redacted] on the MMAS-8 scale.

Scores will be summarised and compared between the treatment groups in an exploratory analysis at each time point.

GSRS

The Gastrointestinal Symptom Rating Scale (GSRS) has 15 items and is divided into four domains: abdominal pain; dyspeptic syndrome; indigestion syndrome; and bowel syndrome. The scale ranges from CCI [redacted] (~~0~~**1**) to CCI [redacted] (7). The overall score is calculated by adding the completed scores of individual items in each group, for a possible total ranging from ~~0~~**15** to 105. Higher scores show greater severity of symptoms [Svedlund, 1988]. The GSRS has been used and validated in other

antiretroviral studies, which examine the GI symptoms associated with boosted PIs [Sáez de la Fuente; 2009; Mtambo, 2013].

9.8. Independent Data Monitoring Committee (IDMC)

The following text has been added:

The IDMC completed pre-planned interim analyses #1 and #2 and following an ad hoc review of trial data prior to interim analysis #3, the IDMC observed significant, clinically relevant differences between treatment arms in favour of DTG. The IDMC recommended that the LPV/RTV treatment arm be discontinued and subjects currently receiving LPV/RTV in the study be switched to a regimen with DTG as the third drug, if considered appropriate by the Investigator. Interim analysis #3 will no longer take place.

10. REFERENCES

The following reference has been added:

WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: Recommendations for a public health approach. Second edition 2016. Available at: http://www.who.int/hiv/pub/arv/arv-2016/en/ (accessed 29 March 2017).

The following references have been updated:

GlaxoSmithKline Document Number ~~RM2007/00683/07~~**RM2007/00683/10**: GSK1349572 Clinical Investigator's Brochure. ~~February 2014~~**October 2016**.

Kaletra EU Summary of Product Characteristics, February ~~2014~~**2017**.

Kaletra US Product Information, November ~~2013~~**2016**.

TIVICAY Summary of Product Characteristics, ~~January 2014~~**February 2017**.

TIVICAY US Product Information, ~~August 2013~~**March 2017**.

11.7.3. Protocol Amendment 03

Protocol changes for Amendment 03, from protocol changes to Amendment 02 (19-Apr-2017)

This protocol amendment applies to all participating sites.

Amendment 03 Summary and Rationale:

Changes were made to the protocol to manage and mitigate risks following identification of a potential safety issue related to neural tube defect in infants born to women with exposure to dolutegravir at the time of conception.

- References to the most recent version of the DTG investigator's brochure and supplements were included.
- The Risk Assessment table (Section 1.3.1) was updated to include language regarding risk and mitigation of neural tube defects.
- Inclusion criterion 2 (Section 4.2) was updated to exclude the double barrier method of contraception, which does not meet updated GSK/ViiV Healthcare criteria for a highly effective method. Acceptable methods of contraception were clarified and provided within the protocol; details of these are no longer provided in the SPM.
- The Withdrawal Criteria (Section 4.5) were updated to include a reminder that females of childbearing potential who change their minds and desire to be pregnant should also be withdrawn from the study.
- The Time and Events Table (Section 6.1). was updated to include a reminder for investigators to check at every visit that females of childbearing potential are avoiding pregnancy.
- The References (Section 10) was updated to include a reference citing methods of highly effective contraception and update the reference to the current DTG Investigator's Brochure.

A list of specific changes is provided below. Unless stated otherwise, new text is represented in bold font, and deleted text in strikethrough font.

List of Specific Changes

Authors

Author(s): PPD
PPD
PPD
PPD

References to Investigator's Brochure and Supplements

The DTG investigator brochure version number was updated in Section 1.1, Section 1.3, and 6.4.4.7, and references to IB supplements were added.

Section 1.3.1 Risk Assessment

An additional risk and mitigation strategy was added to the table in this section as shown below.

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy[1]
Investigational Product (IP) [DTG] Refer to IB for additional information on 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, and, if she is a female of childbearing potential, agrees to follow one of the options for prevention of pregnancy listed in the Inclusion Criterion 2 (see Section 4.2) during treatment with study drug and until at least 2 weeks after the last dose of study medication. 2. Women who become pregnant, or who desire to be pregnant while in the study will have study treatment discontinued and be withdrawn from the study. 3. Females of childbearing potential are reminded re: pregnancy avoidance and adherence to contraception requirements at every study visit. 4. Pregnancy status is monitored at every study visit.**

Section 4.2 Inclusion Criteria, inclusion criterion 2

2. A female subject may be eligible to enter and participate in the study if she:

   a. is of non-childbearing potential defined as either post-menopausal (12 months of spontaneous amenorrhea and ≥45 years of age) or physically incapable of becoming pregnant with documented tubal ligation, hysterectomy, or bilateral oophorectomy or,

   b. is of child-bearing potential, with a negative pregnancy test at both Screening and Day 1 and agrees to use one of the following methods of contraception to avoid pregnancy **throughout the study and for at least 2 weeks after discontinuation of all study medication**:

      - Complete abstinence from intercourse from 2 weeks prior to administration of IP~~, throughout the study, and for at least 2 weeks after discontinuation of all study medications~~.
      - ~~Double barrier method (male condom/spermicide, male condom/diaphragm, diaphragm/spermicide).~~
      - Approved hormonal contraception for subjects randomised to the DTG arm ~~(see the SPM for a listing of examples of approved hormonal contraception)~~, **including:**
        - **Combined oestrogen and progestogen oral contraceptive [Hatcher, 2011])**
        - **Contraceptive subdermal implant**
        - **Injectable progestogen [Hatcher, 2011]**

- **Contraceptive vaginal ring [Hatcher, 2011]**
- **Percutaneous contraceptive patches [Hatcher, 2011]**

- Approved hormonal contraception **(as for subjects randomised to the DTG arm; see above)** and a barrier method for subjects randomised to the LPV/RTV arm ~~(see the SPM for a listing of examples of approved hormonal contraception)~~.
- **Intrauterine device or intrauterine system.** ~~Any intrauterine device (IUD) with published data showing that the expected failure rate is <1% per year (not all IUDs meet this criterion, see the SPM for an example listing of approved IUDs). Any intrauterine device (IUD) with published data showing that the expected failure rate is <1% per year (not all IUDs meet this criterion, see the SPM for an example listing of approved IUDs).~~
- 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.**
- Any other method with published data showing that the expected failure rate is <1% per year.

Any contraception method must be used consistently and in accordance with the approved product label. **The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. Note: these contraceptive requirements do not apply to females of childbearing potential with same sex partners only, when this is their preferred and usual lifestyle.**

Section 4.5 Withdrawal/Stopping Criteria, last bullet

- Pregnancy (intrauterine), regardless of termination status of pregnancy **(Section 6.4.11). As a reminder, females of childbearing potential who changed their minds and desire to become pregnant, or who state they are no longer willing to comply with the approved pregnancy avoidance methods, should also be withdrawn from the study**.

Section 6.1 Time and Events Table

Table 1

Footnote 'o' was revised as shown below:
o. Pregnancy testing will be conducted (women of child bearing potential only) on serum (S) samples with the exception of Day 1, which must be a urine (U) test to confirm status prior to administration of IP. **Remind females of childbearing potential of the need to**

avoid pregnancy while on study and adherence to the study's contraception requirements.

Section 10 References

The following reference has been updated:

GlaxoSmithKline Document Number RM2007/00683/~~10~~**11**: GSK1349572 Clinical Investigator's Brochure**, Version 11**. October ~~2016~~**2017**.

The following additional references were included:

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

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

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