TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A Phase IIIb, randomized, open-label study of the safety and efficacy of dolutegravir/abacavir/lamivudine once daily compared to atazanavir and ritonavir plus tenofovir/emtricitabine once daily in HIV-1 infected antiretroviral therapy naïve women

Compound Number: GSK1349572+GR109714+GI265235 (GSK2619619)

Effective Date: 19-JUN-2018

Protocol Amendment Number: 03

Subject: HIV infection, integrase inhibitor, dolutegravir/abacavir/lamivudine fixed dose combination, once daily, atazanavir, ritonavir, tenofovir/emtricitabine, antiretroviral therapy naïve, women

Authors: PPD

Revision Chronology:

2013N161649_00	2013-MAY-31	Original
2013N161649_01	2013-AUG-12	Amendment No. 01
This amendment includes the removal of the Child-Pugh Classification due to its unsuitability for use in subjects with no known hepatic impairment. Other minor clarifications and corrections have been incorporated, including an update to Figure 2, Virologic Criteria for Subject Management at Week 24, to differentiate between the two scenarios for re-testing HIV-1 RNA levels.		
2013N161649_02	2014-AUG-11	Amendment No. 2
Changes made to the UK country specific information on study duration (Appendix 5) to comply with requests from the UK MHRA. The medical monitor contact information has also been updated		
2013N161649_03	2018-JUN-19	Amendment No. 3
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. • 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, and refer to the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential. • The withdrawal criteria (Section 4.5.) were updated to include a reminder that females of reproductive potential who change their minds and desire to be pregnant, or who state they no longer are willing to comply with the approved pregnancy avoidance methods, should also be withdrawn from the study. • The Time and Events table (Section 6.1.) was updated to include a reminder for investigators to check at every visit that females of reproductive potential are avoiding pregnancy. • Appendix 6 was added: Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential Administrative updates were made.		

SPONSOR SIGNATORY

PPD

PPD

Kimberly Y. Smith PPD MPI PPD
Vice President and
Global Research and Medical
ViiV Healthcare

Date

PPD

SPONSOR INFORMATION PAGE

Clinical Study Identifier: ING117172

This study is sponsored by ViiV Healthcare. GlaxoSmithKline is responsible for implementing and managing all aspects of this study.

Sponsor Legal Registered Address:

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

Sponsor Contact Address:

ViiV Healthcare
Five Moore Drive
Research Triangle Park, North Carolina USA
27709-3398
Telephone: +1 877 844 8872

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.

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

PPD MD
ViiV Healthcare,
5 Moore Drive,
Research Triangle Park, NC 27709, USA
Mobile: PPD
Facsimile: PPD
e-mail: PPD

Regulatory Agency Identifying Numbers:

US IND: 114,820
EudraCT: 2012-005823-34

INVESTIGATOR AGREEMENT PAGE

For protocol number ING117172

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 clinical study.

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

Investigator Name: _____

Investigator Signature	Date

TABLE OF CONTENTS

PAGE

LIST OF ABBREVIATIONS

3TC	Lamivudine, EPIVIR
AE	Adverse Event
ABC	Abacavir, ZIAGEN
ABC/3TC	Abacavir/Lamivudine, EPZICOM, KIVEXA
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine Aminotransferase
ART	Antiretroviral Therapy
AST	Aspartate Aminotransferase
ATV	Atazanavir, Reyataz
BID	Twice Daily
BUN	Blood urea nitrogen
c/mL	Copies/milliliter
CC	Calcium carbonate
CD4+	Helper-inducer T-lymphocyte having surface antigen CD4 (cluster of differentiation 4)
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
COBI	Cobisistat
CPK	Creatine Phosphokinase
CrCL	Creatinine clearance
CRF	Case Report Form
CSR	Clinical Study Report
C-SSRS	Columbia Suicidality Severity Rating Scale
DAIDS	Division of Acquired Immunodeficiency 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
FDC	Fixed dose combination
FF	Ferrous Fumerate
FRP	Females of Reproductive Potential
FTC	Emtricitabine
GCP	Good Clinical Practices
GCSP	Global Clinical Safety and Pharmacovigilance
GFR	Glomerular filtration rate
GI	Gastrointestinal
GSK	GlaxoSmithKline
HBsAg	Hepatitis B Virus surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL	High Density Lipoprotein

HIV-1	Human Immunodeficiency Virus Type 1
HIVTSQ	HIV Treatment Satisfaction Questionnaire
HLA	Human Leukocyte Antigen
HRQoL	Health Related Quality of Life
HSR	Hypersensitivity Reaction
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
INI	Integrase inhibitor
IP	Investigational Product
IRB	Institutional Review Board
IRIS	Immune Reconstitution Inflammatory Syndrome
ITT	Intent to Treat
IUD	Intrauterine Device
LDH	Lactic Dehydrogenase
LDL	Low Density Lipoprotein
LLOD	Lower Limit of Detection
LSLV	Last subject's last visit
MAA	Marketing Application Authorisation
MCS	Mental Component Summary
MCV	Mean Corpuscular Volume
MSDS	Material Safety Data Sheet
mg	Milligram
mL	Milliliter
NCEP	National Cholesterol Education Program
NRTI	Nucleoside Reverse Transcriptase Inhibitor
PCS	Physical Component Summary
PGx	Pharmacogenetic
PK	Pharmacokinetic
Pol	Polymerase
PP	Per Protocol
PRO	Protease
PRTD	Proximal Renal Tubule Dysfunction
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
SF-12	12-Item Short Form Health Survey
SJS	Stevens Johnson Syndrome
SPM	Study Procedure Manual
STR	Single Tablet Regimen
TEN	Toxic Epidermal Necrolysis

TDF	Tenofovir disoproxil fumarate, Viread
TLOVR	Time to Loss of Virologic Response
ULN	Upper limit of normal
VSLC	ViiV Safety and Labeling Committee
WBC	White blood cells

Trademark Information

Trademarks of ViiV Healthcare
EPIVIR
EPZICOM
KIVEXA
TRIZIVIR
ZIAGEN

Trademarks not owned by ViiV Healthcare
Atripla (efavirenz/tenofovir/emtricitabine)
Complera (rilpivirine/tenofovir/ emtricitabine)
GenoSure
Isentress (raltegravir)
Monogram Biosciences
Norvir (ritonavir)
Phenosense
Quest Diagnostics
Reyataz (atazanavir)
Stribild (elvitegravir/cobicistat/ tenofovir/emtricitabine)
Truvada (tenofovir/emtricitabine)

PROTOCOL SUMMARY

Rationale

The dolutegravir, abacavir and lamivudine fixed dose combination (DTG/ABC/3TC FDC) may provide a better treatment option for women infected with Human Immunodeficiency Virus Type 1 (HIV-1) due to its robust antiviral activity, safety profile, high barrier to resistance, low potential for drug-drug interactions, and administration as a once-daily single tablet regimen (STR). Currently available integrase inhibitors (INIs), elvitegravir (ELV) and raltegravir (RAL), have limitations including the development of clinical resistance, the need for a twice daily (BID) regimen for RAL administration, and a pharmacokinetic (PK) booster for ELV administration, which leads to an increased potential for drug-drug interactions including with oral contraceptives. Only limited data on DTG in women are available in Phase III studies due to lower enrollment of women compared with men. Therefore, a powered study of DTG in a single tablet regimen with ABC and 3TC will be conducted in women to provide robust data on safety and efficacy in this population.

Study ING117172 is a Phase IIIb trial designed to demonstrate the non-inferior antiviral activity of DTG/ABC/3TC FDC once daily compared to atazanavir plus ritonavir (ATV+RTV) and tenofovir disoproxil fumarate/emtricitabine fixed dose combination (TDF/FTC FDC) all administered once daily in HIV-1 infected, antiretroviral therapy (ART)-naïve women over 48 weeks. This study will also characterize the safety and tolerability of DTG/ABC/3TC FDC compared to ATV+RTV+TDF/FTC FDC.

Objectives

Primary Objective

- To demonstrate the non-inferior antiviral activity of DTG/ABC/3TC FDC once daily compared to ATV+RTV+TDF/FTC FDC each administered once daily over 48 weeks in HIV-1 infected ART-naïve women.

Secondary Objectives

- To evaluate the antiviral and immunological activity and incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome [AIDS] and death) of DTG/ABC/3TC FDC once daily compared to ATV+RTV+TDF/FTC FDC once daily over time;

- To compare the safety, tolerability, and laboratory parameters of DTG/ABC/3TC FDC once daily to ATV+RTV+TDF/FTC FDC once daily over time;

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

- To evaluate renal markers (in urine and blood), and bone markers (in blood) in subjects treated with DTG/ABC/3TC FDC compared to ATV+RTV+TDF/FTC FDC;

- To assess treatment satisfaction, and change in health-related quality-of-life for subjects treated with DTG/ABC/3TC FDC compared to ATV+RTV+TDF/FTC FDC;

- To evaluate the effect of patient characteristics (i.e., demographic factors, HIV-1 subtype, Baseline CD4) on response to DTG/ABC/3TC FDC compared to ATV+RTV+TDF/FTC FDC over time.

Study Design

This study is a Phase IIIb randomized, open-label, active-controlled, multicenter, parallel group, non-inferiority study. The study will be conducted in approximately 474 HIV-1 infected ART-naïve women. Subjects will be randomized 1:1 to receive a FDC of DTG 50mg/ ABC 600mg/ 3TC 300mg once daily or ATV 300mg plus RTV 100mg and TDF 300mg/ FTC 200mg FDC each administered once daily. Randomization will be stratified by Screening plasma HIV-1 RNA (≤100,000 copies/mL [c/mL] or >100,000 c/mL) and CD4+ cell count (≤350 cells/mm^3 or >350 cells/mm^3). The study will comprise a Screening Phase (approximately 14-28 days), a Randomized Phase (48 weeks), and a Continuation Phase. The primary analysis will take place after the last subject completes 48 weeks of therapy. No dose reductions, modifications in dosage, or changes in the frequency of dosing of any components of each regimen will be allowed in this study.

Subjects randomized to receive DTG/ABC/3TC FDC who successfully complete 48 weeks of treatment will continue to have access to DTG/ABC/3TC FDC (Continuation Phase) until it is either locally approved and commercially available, the patient no longer derives clinical benefit, the patient meets a protocol-defined reason for discontinuation, or development of DTG/ABC/3TC FDC is terminated. Subjects randomized to the ATV+RTV+TDF/FTC arm will receive ATV+RTV+TDF/FTC FDC through their Week 48 visit only, after which they will complete the study and will need to have alternate arrangements in place to access antiretroviral medication.

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: the proportion of subjects with plasma HIV-1 RNA <50 c/mL and <400 c/mL over time; absolute values and change from Baseline in plasma HIV-1 RNA over time; absolute values and changes from Baseline in CD4+ cell counts over time, and incidence of disease progression (HIV-associated conditions, AIDS and death).

Safety endpoints will include: incidence and severity of adverse events (AEs) and laboratory abnormalities; the proportion of subjects who discontinue treatment due to AEs; absolute values and changes over time in laboratory parameters; change from Baseline in fasting lipids and glucose; changes from Baseline in renal and bone markers.

Heath outcomes endpoints will include: Change from Baseline in health related quality of life using SF-12 at Week 48, and treatment satisfaction (using the HIV Treatment Satisfaction Questionnaire) for subjects treated with DTG/ABC/3TC FDC and those treated with ATV+RTV+TDF/FTC FDC at weeks 4, 12, 24, and 48 (or withdrawal from the study).

Virology endpoints will include the incidence of treatment emergent genotypic and phenotypic resistance in subjects who meet 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 DNA of the host cell. Since integration is a vital 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 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 as part of a single tablet regimen (STR) with cobicistat (COBI), tenofovir (TDF), and emtricitabine (FTC, [Stribild Package Insert, 2012]).

While RAL and ELV have shown potent antiviral activity in treatment-naïve and treatment-experienced patients, there are limitations to both these medications. Clinical resistance to both RAL and ELV has been reported from Phase II studies in treatment-experienced patients [Hazuda, 2007; McColl, 2007] and from Phase III studies in both treatment-experienced [Cooper, 2008; Molina J, 2012] and treatment-naïve subjects [Lennox, 2010; Sax, 2012; DeJesus, 2012]. In addition, RAL requires twice daily (BID) dosing and is currently not available in a fixed dose combination (FDC) regimen. ELV requires co-administration with a pharmacokinetic (PK) booster, such as ritonavir (RTV) or COBI. Furthermore, ELV-containing regimens had higher rates of gastrointestinal (GI) adverse events (AEs) than a RAL-containing regimen and Atripla (a FDC of efavirenz [EFV]/TDF/FTC [Atripla, April 2013]) in treatment-experienced and treatment-naïve patients, respectively [Molina J, 2012; Sax, 2012]; Stribild is also not recommended for patients with creatinine clearance (CrCL) under 70 mL/min. Because of the cobicistat in Stribild, there are also numerous drug interactions due to inhibition of cytochrome P450 3A4. Therefore, development of new INIs with an improved safety and resistance profile, and improved dosing administration is desirable.

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 (and therefore lacks the associated drug interactions, specifically with oral contraceptives).

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 summarized in the DTG Investigator Brochure (IB [GlaxoSmithKline Document Number [GSK Document Number RM2007/00683/11, GSK Document Number 2017N352880_00, GSK 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 generally favorable to Atripla and EFV (studies ING113086 [SPRING-2], ING114467 [SINGLE] and ING111762

[SAILING]). The most frequently observed AEs across patient populations were diarrhea, 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 an efficacious dose, and non-inferior to RAL in combination with a background regimen with dual nucleoside reverse transcriptase inhibitor (NRTI) [SPRING-2]. When used in combination with abacavir/lamivudine (ABC/3TC, EPZICOM/KIVEXA™), DTG was shown to be superior to EFV/TDF/FTC, a result driven by better tolerability of the DTG based regimen [SINGLE]. Phase III studies have also demonstrated excellent antiviral activity of DTG in INI-naïve treatment experienced patients, and in patients with INI resistance in studies ING111762 [SAILING] and ING112574 [VIKING-3], respectively. 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 and significantly fewer subjects with INI resistance were observed when compared with RAL. Data from two further Phase III studies [SPRING-2 and SINGLE] in treatment-naive subjects are also supportive of a high barrier to resistance.

HIV continues to be the leading cause of death and disease among women of reproductive age worldwide, particularly among women of ethnic/racial minorities. While women comprise approximately 50% of patients infected with HIV globally, the number of women in most HIV clinical trials remains low, and recruiting and retaining women into antiretroviral clinical studies remains a challenge. The reasons are multiple, but may reflect differences in lifestyle, care commitments, behavior and socioeconomics between women and men infected with HIV. Additionally, comparator regimens in many studies do not include commonly recommended regimens for women of child bearing potential, so pregnancy avoidance strategies are stringent.

In Phase IIIa studies of DTG in treatment naïve subjects, women comprised 15% and 16% respectively of the randomized populations in the SPRING-2 and SINGLE studies, for a total of 130 women randomized to DTG. In the SPRING-2 study, DTG was non-inferior to RAL overall and similar efficacy was observed across gender. In the SINGLE study, DTG+ABC/3TC FDC demonstrated superior efficacy to EFV/TDF/FTC, and the treatment differences by gender were consistent with the overall treatment difference.

The GRACE study is the only prospective clinical study with published data to date powered to assess gender differences in efficacy and safety [Currier 2010]. In this study of darunavir and RTV (DRV+RTV) in combination with optimized background therapy in ART-experienced subjects, the virologic response rate was lower in women than in men, and women had significantly higher rates of discontinuation (33%) compared to men (23%). Nausea and vomiting was also more common in women. Other non-powered studies have seen increased rates of discontinuation and AEs in women compared to men (e.g., the CASTLE study [Molina, 2008]).

Evaluation of the safety, tolerability and efficacy of antiretroviral agents in women is important to appropriately inform clinicians and patients about their therapy. Women may metabolize and respond to antiretroviral agents differently than men; women may have higher drug exposure, be at greater risk for some adverse events (i.e., lactic acidosis,

hepatotoxicity/rash, and osteoporosis), and have a higher potential for drug interactions (i.e., oral hormonal contraceptives/or estrogen).

FDCs and STRs have greatly simplified the treatment of patients with HIV, and may be of greater importance in patients with lifestyles or care commitments that may impair adherence to dosing schedules, including some women and those in underserved populations. In a study by Paterson et. al. [Paterson, 1999], a linear relationship between levels of adherence and viral load suppression was observed. Adherence to therapy is essential to achieve viral suppression and prevent emergence of resistance mutations. Among regimens of comparable efficacy, physicians and HIV-1 infected patients who receive ART rate total pill burden, dosing frequency, and safety concerns among the greatest obstacles to achieving adherence. Drug resistant virus eventually emerges in most patients who struggle with consistent adherence. To achieve successful long-term treatment, the prevention of drug resistance has become the most significant challenge. DTG/ABC/3TC FDC is being developed to address the needs for a FDC with an INI and ABC/3TC.

1.2. Rationale

The DTG/ABC/3TC FDC may provide a better treatment option for women infected with HIV-1 due to its robust antiviral activity, safety profile, high barrier to resistance, low potential for drug-drug interactions, and administration as a once-daily STR. Currently available integrase inhibitors, ELV and RAL, have limitations including the development of clinical resistance, the need for a BID regimen for RAL administration, and a PK booster for ELV administration, which leads to an increased potential for drug-drug interactions including with oral contraceptives. Only limited data on DTG in women are available in Phase III studies due to lower enrollment of women compared with men. Therefore, a powered study of DTG in a STR with ABC and 3TC will be conducted in women to provide robust data on safety and efficacy in this population.

Study ING117172 is a Phase IIIb trial designed to demonstrate the non-inferior antiviral activity of DTG/ABC/3TC FDC once daily to atazanavir plus ritonavir (ATV+RTV) and TDF/FTC FDC all administered once daily in HIV-1 infected, ART-naïve women over 48 weeks. This study will also characterize the safety and tolerability of DTG/ABC/3TC FDC compared to ATV+RTV+TDF/FTC FDC.

The rationale for selection of the active comparator, ATV+RTV with TDF+FTC, is provided in the Section 3.2.

1.2.1. Principle of Dose Selection

Dose selection was determined in ING112276 (SPRING-1). This was a dose-ranging Phase IIb study to evaluate the long-term antiviral activity and safety of DTG at doses of 10, 25, and 50 mg once daily in combination with two NRTIs in HIV-infected, treatment-naïve adult subjects. The dose selection strategy for DTG was to select the maximum tolerated dose from this study to take forward in to further evaluation in INI-naive subjects. If comparable efficacy, safety and tolerability were observed across all three DTG doses, the 50 mg dose would be selected for further investigation in Phase III.

Based on comparison of virological markers of HIV infection in the SPRING-1 study, the proportion of subjects who achieved the primary endpoint (HIV-1 RNA <50 copies/mL [c/mL], by Time to Loss of Virologic Response [TLOVR] algorithm) by Week 16 was consistently high across the DTG dose arms (≥90%) with a low rate of confirmed virologic failure. As summarized in the DTG IB, this activity has been maintained in all three dosing arms through Week 96 [GSK Document Number RM2007/00683/11, GSK Document Number 2017N352880_00, GSK Document Number 2017N352880_01].

DTG was well tolerated across all doses studied. A good safety and tolerability profile with a low discontinuation rate due to AEs was observed in all three dose arms with no significant dose-dependent trends in safety parameters. Hence, the DTG 50 mg once daily dose was selected for Phase III studies in treatment-naïve adult subjects.

The efficacy and safety of DTG 50mg once daily was confirmed in the Phase III program.

1.2.2. Impact of Potential Drug-Drug Interaction

Due to a different route of elimination, no drug interaction is expected between DTG and ABC/3TC. DTG is metabolized through UGT1A1. 3TC is primarily eliminated by renal mechanisms with the majority of drug eliminated unchanged in the urine. ABC is metabolized by glucuronidation and by alcohol dehydrogenase with less than 2% excreted in the urine as unchanged parent. ABC does not have inhibitory activity on UGT pathways and is metabolized primarily through UGT2B7. Only 25-36% of ABC is glucuronidated, indicating it is not a substrate sensitive route. Furthermore, UGT is a high capacity enzyme system and the fraction metabolized by UGT pathways for both of these compounds is likely less than 50%. Finally, no differences in DTG PK were observed for subjects receiving TDF/FTC versus ABC/3TC in SPRING-1 (ING112276).

For further information refer to the most current version of the IB for DTG [GSK Document Number RM2007/00683/11, GSK Document Number 2017N352880_00, GSK Document Number 2017N352880_01]. Relevant data on use of calcium and iron supplements with DTG are provided below.

1.2.2.1. Use of calcium and iron supplements with dolutegravir

Study ING116898 was a Phase I, open label, randomized, four-period crossover study to evaluate the effects of calcium carbonate (CC) 1200 mg and ferrous fumarate (FF) 325 mg on PK of DTG 50 mg in healthy adult subjects.

Study Design: 12 subjects were enrolled into one of the two cohorts and received each of four treatments in a randomized fashion: 1) A single dose of DTG 50 mg administered under fasted conditions; 2) A single dose of DTG 50 mg co-administered with a single dose of CC 1200 mg or FF 324 mg under fasted conditions; 3) A single dose of DTG 50 mg co-administered with a single dose of CC or FF with a moderate-fat meal; 4) A single dose of DTG 50 mg administered under fasted conditions 2 hours prior to administration of a single dose of CC or FF. There was a washout period of at least

7 days between treatments. Serial PK samples were collected during each treatment period for the measurement of plasma DTG concentrations.

Results: Under fasted conditions, co-administration of CC reduced DTG exposure by 37-39% and FF reduced DTG exposure by 54-57%; food (a moderate fat meal) and 2 hour separation completely eliminated the negative effect of calcium carbonate on DTG exposure.

Table 1 Statistical Comparison of Plasma DTG Pharmacokinetic Parameters (Calcium Carbonate Cohort)

Comparison	Ratio of GLS Means (90% CI)			
	DTG + CC vs DTG Alone (fasted)	DTG + CC (fed) vs DTG Alone (fasted)	DTG 2hr prior to CC vs DTG Alone (fasted)	DTG + CC (fed) vs DTG+ CC (fasted)
AUC(0-t)	0.61 (0.48, 0.79)	1.10 (0.84, 1.43)	0.95 (0.73, 1.24)	1.79 (1.37, 2.33)
AUC(0-∞)	0.61 (0.47, 0.79)	1.09 (0.84, 1.43)	0.94 (0.72, 1.23)	1.78 (1.36, 2.33)
Cmax	0.63 (0.50, 0.81)	1.07 (0.83, 1.38)	1.00 (0.78, 1.29)	1.70 (1.32, 2.18)
C24	0.61 (0.47, 0.80)	1.08 (0.81, 1.42)	0.90 (0.68, 1.19)	1.76 (1.33, 2.33)

CI = confidence interval

Table 2 Statistical Comparison of Plasma DTG Pharmacokinetic Parameters (Ferrous Fumarate Cohort)

Comparison	Ratio of GLS Means (90% CI)			
	DTG + FF vs DTG Alone (fasted)	DTG + FF (fed) vs DTG Alone (fasted)	DTG 2hr prior to FF vs DTG Alone (fasted)	DTG + FF (fed) vs DTG+ FF (fasted)
AUC(0-t)	0.45 (0.37, 0.54)	0.98 (0.81, 1.19)	0.94 (0.78, 1.14)	2.18 (1.80, 2.64)
AUC(0-∞)	0.46 (0.38, 0.56)	0.97 (0.80, 1.19)	0.95 (0.78, 1.15)	2.12 (1.75, 2.58)
Cmax	0.43 (0.35, 0.52)	1.03 (0.85, 1.26)	0.99 (0.81, 1.21)	2.40 (1.97, 2.94)
C24	0.44 (0.36, 0.54)	0.99 (0.80, 1.22)	0.92 (0.74, 1.13)	2.25 (1.83, 2.77)

Conclusions: DTG can be given concurrently with calcium or iron supplements with food; without food, DTG should be given 2 hours prior to or 6 hours after calcium or iron supplements.

1.3. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with DTG can be found in the most current version of the DTG IB. The following section outlines the risk assessment and mitigation strategy primarily for DTG in the DTG/ABC/3TC FDC in this protocol. For ABC, 3TC, ATV, RTV and TDF/FTC, the approved country product labels should be referenced. The comparator regimen, ATV+RTV + TDF/FTC FDC, is a preferred/recommended treatment regimen for HIV-infected ART naive subjects according to current guidelines [DHHS, 2013; EACS, 2012].

1.3.1. Risk Assessment

There are no shared metabolism pathways between the components of DTG/ABC/3TC, and no common target organs were identified in respective pre-clinical studies. As such, there is no pharmacologic data that would predict increased safety risk for the DTG/ABC/3TC formulation beyond that identified for the individual active moieties DTG, ABC and 3TC. Early in clinical development, no drug-drug interaction between DTG and ABC/3TC was apparent given the safety and efficacy profile observed in the Phase IIb study ING112276 [SPRING-1] in which 67 subjects received DTG in combination with ABC/3TC for up to 96 weeks. Clinical safety data from the subjects treated with DTG + ABC/3TC in the pivotal ING114467 [SINGLE] and supporting study ING113086 were consistent with the safety profile of the individual active moieties.

All medications have AE profiles that must be assessed prior to use, allowing for an appropriate risk/benefit assessment. Considerations when using DTG/ABC/3TC are as follows:

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy[1]
Investigational Product (IP) [DTG/ABC/3TC] Refer to IB for additional information on DTG and DTG/ABC/3TC Refer to approved country product label for additional information on ABC/3TC		
Hypersensitivity (including abacavir hypersensitivity reaction [ABC HSR]) and rash	A well characterised, idiosyncratic, drug-related HSR is the most important risk associated with ABC (Section 6.4.4.9). Exclusion of individuals found to carry the Human Leukocyte Antigen (HLA)-B*5701 allele from ABC therapy reduces the risk of HSR. Rash, including Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and Erythema Multiforme have been reported in patients taking ABC (See Section 6.4.4.9 and Section 6.4.4.10). HSR has been observed uncommonly with DTG. Rash was commonly reported in DTG Phase IIb/III clinical trials; episodes were generally mild to moderate in intensity; no episodes of severe rash, such as SJS, TEN and Erythema Multiforme were reported. Data on HSR for DTG and DTG+ABC/3TC FDC suggest that there will not be additional risk from HSR in HLA-B*5701 negative subjects receiving the DTG/ABC/3TC FDC	Subjects positive for HLA-B*5701 are excluded from participating. Additionally, 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 suspected HSR with DTG (Section 6.4.4.8) or ABC (Section 6.4.4.9), and skin reactions without systemic involvement (Section 6.4.4.10). The subject informed consent form includes information on this risk and the actions subjects should take in the event of a HSR or associated signs and symptoms. Subjects are to be reminded to read the ABC HSR Warning Card accompanying their study medication and of the importance of keeping this card with them at all times.
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. Current treatment guidelines [DHHS, 2013; EACS 2012] do not recommend monotheraphy with 3TC for patients with HBV infection, which is what subjects randomized to DTG/ABC/3TC would effectively be receiving. Additionally, discontinuation of 3TC in HBV coinfected subjects can result in severe exacerbations of HBV.	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 positive for HBV at screening (hepatitis B virus surface antigen positive [+HBsAg]), or with an anticipated need for HCV therapy during the study 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]
Theoretical serious drug interaction with dofetilide	Co-administration of DTG may increase dofetilide plasma concentration via inhibition of OCT2 transporter, resulting in potentially life-threatening toxicity.	The co-administration of DTG with dofetilide is prohibited in the study (Section 5.6.2).
GI intolerance	Non-clinical studies showed upper and lower GI toxicity, including vomiting, diarrhea and gastric erosions observed in monkey toxicology studies (thought to be related to local and not systemic toxicity). Mild to moderate GI intolerance (mainly diarrhea and nausea) is associated with DTG treatment in a small proportion of 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 OCT-2 receptor. DTG has been shown to have no significant effect on glomerular filtration rate (GFR) or effective renal plasma flow. Measurement of albumin/creatinine ratio confirmed there was no difference in the effect of DTG on albumin excretion compared with EFV or RAL. 3TC is eliminated by renal excretion and exposure increases in patients with renal dysfunction.	Due to requirements for dose reduction of 3TC in patients with renal dysfunction, subjects with a CrCL <50 mL/min are excluded (Section 4.3). Specific/detailed toxicity management guidance is provided for subjects who develop a decline in renal function (including proximal renal tubule dysfunction; Section 6.4.4.6) and/or proteinuria (Section 6.4.4.7).
Psychiatric disorders	Psychiatric disorders including suicide ideation and behaviors are common in HIV infected patients. The psychiatric profile for DTG (including suicidality, depression, bipolar and hypomania, anxiety and abnormal dreams) was similar or favorable compared with other ART. 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 behavior (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 6.4.4.5).

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy[1]
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. The increased risk for HBV and HCV IRIS with DTG- containing ART is addressed above; there was a low rate of other medical conditions frequently implicated in IRIS cases.	Subjects positive for HBsAb at screening or with active HCV illness (anticipated to require therapy) are excluded from participating. Subjects will have routine laboratory monitoring
Use in pregnancy	The safe use of DTG in human pregnancy has not been established. DTG has been shown to cross the placenta in reproductive toxicity studies in animals. DTG has not been associated with findings in animal reproductive studies.	Women who are pregnant will be excluded from the study (Section 4.3). Females of childbearing potential are required to have a negative pregnancy test at both Screening and Day 1 of the study and agree to use one of the methods documented in Section 4.2. to avoid pregnancy during the study. Females of childbearing potential will have pregnancy tests performed at all scheduled clinic visits. Pregnant women will be withdrawn from this study and their pregnancy followed to determine outcome (including premature termination) and status of mother and child.
DTG: Neural tube defects	In one ongoing birth outcome surveillance study in Botswana, early results from an unplanned interim analysis show that 4/426 (0.9%) of women who were taking DTG when they became pregnant had babies with neural tube defects compared to a background rate of 0.1%.	1. A female subject is eligible to participate if she is not pregnant, not lactating, and, if she is a female of reproductive potential, agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see Appendix 6, Section 11.6), until at least 2 weeks after discontinuation of IP 2. Women who are breastfeeding or plan to become pregnant or breastfeed during the study are excluded; 3. Women who become pregnant, or who desire to be pregnant while in the study, or who state they no longer are willing to comply with the approved pregnancy avoidance methods, will have study treatment discontinued and withdrawn from the study. 4. Females of reproductive potential are reminded re: pregnancy avoidance and adherence to contraception requirements at every study visit. 5. Pregnancy status is monitored at every study visit

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 Immunodeficiency 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 approximately a monthly basis (switching to approximately quarterly reviews upon reaching the primary endpoint); 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

The DTG/ABC/3TC FDC provides a convenient once daily STR, 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).

A regimen comprised of DTG administered with ABC/3TC has been shown to be highly efficacious and well tolerated in treatment-naive subjects. In the Phase 3 double-blind SINGLE study (ING114467), 833 therapy-naive adults were randomized to DTG 50 mg plus ABC/3TC once daily or a guidelines-preferred STR of EFV/TDF/FTC once daily. At Week 48, the proportion of subjects with HIV-1 RNA <50 c/mL in the DTG+ABC/3TC arm (88%) was superior to the EFV/TDF/FTC arm (81%), P=0.003. Time to viral suppression (median 28 vs. 84 days; P<0.001) and increases in CD4 cell counts (+267.1 vs. +208.2 cells/mm3; P<0.001) also favored DTG+ABC/3TC. No subjects on DTG+ABC/3TC had detectable antiviral resistance; 1 TDF-associated and 4 EFV-associated mutations were detected in EFV/TDF/FTC subjects with viral failure. In a by gender analysis, Week 48 responses in women (85%) were higher in recipients of DTG + ABC/3TC when compared to EFV/TDF/FTC (75%). The overall proportion of subjects discontinuing for adverse events was lower with DTG+ABC/3TC (2%) than EFV/TDF/FTC (10%); rash and neuropsychiatric events (including abnormal dreams, anxiety, dizziness, and somnolence) were significantly more common on EFV/TDF/FTC, whereas insomnia was reported more frequently on DTG+ABC/3TC.

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

1.3.3. Overall Benefit:Risk Conclusion

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with the DTG/ABC/3TC FDC are justified by the anticipated benefits that may be afforded to women with HIV infection.

2. OBJECTIVES

Primary Objective

- To demonstrate the non-inferior antiviral activity of DTG/ABC/3TC FDC once daily compared to ATV+RTV+TDF/FTC FDC each administered once daily over 48 weeks in HIV-1 infected ART naïve women.

Secondary Objectives

- To evaluate the antiviral and immunological activity and incidence of disease progression (HIV-associated conditions, AIDS and death) of DTG/ABC/3TC FDC once daily compared to ATV+RTV+TDF/FTC FDC once daily over time;

- To compare the safety, tolerability, and laboratory parameters of DTG/ABC/3TC FDC once daily to ATV+RTV+TDF/FTC FDC once daily over time;

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

- To evaluate renal markers (in urine and blood), and bone markers (in blood) in subjects treated with DTG/ABC/3TC FDC compared to ATV+RTV+TDF/FTC FDC;

- To assess treatment satisfaction, and change in health-related quality-of-life for subjects treated with DTG/ABC/3TC FDC compared to ATV+RTV+TDF/FTC FDC;

- To evaluate the effect of patient characteristics (i.e., demographic factors, HIV-1 subtype, Baseline CD4) on response to DTG/ABC/3TC FDC compared to ATV+RTV+TDF/FTC FDC over time.

3. INVESTIGATIONAL PLAN

3.1. Study Design

This study is a 48 week Phase IIIb randomized, open-label, active-controlled, multicenter, parallel group, non-inferiority study. The study will be conducted in approximately 474 HIV-1 infected ART-naïve women. Subjects will be randomized 1:1 to receive a DTG/ABC/3TC FDC 50mg/600mg/300mg once daily or ATV (300mg) +RTV (100mg) +TDF/FTC FDC (300mg/200mg) all administered once daily. The primary analysis will take place after the last subject completes 48 weeks on therapy. No dose reductions, modifications in dosage, or changes in the frequency of dosing will be allowed in this study.

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

Screening Period

Randomization may occur as soon as all Screening procedures have been completed and results are available and on file. The 14-day screening period may be extended to 28 days to allow receipt of all Screening assessment results and to accommodate scheduling.

Randomized Phase: Day 1 to Week 48

Subjects who fulfill eligibility requirements will be randomized 1:1 to receive DTG/ABC/3TC FDC once daily or ATV+RTV+TDF/FTC FDC each administered once daily. In order to achieve balance across the two treatment groups of the study, randomization will be stratified by Screening plasma HIV-1 RNA (≤100,000 c/mL or >100,000 c/mL), and CD4+ cell count (≤350 cells/mm^3 or >350 cells/mm^3).

During the Randomized Phase, subjects will attend the clinic at Baseline/Day 1 and at Weeks 4, 12, 24, 36 and 48 of treatment. Additional contacts will be made at Weeks 8, 18, 30 and 42 of treatment, primarily to confirm subjects' understanding of the study

procedures and management of the treatment regimen; these contacts may be conducted via telephone, or as clinic or home visits (or other type of visit as agreed with GSK).

DTG/ABC/3TC FDC Continuation Phase

Subjects randomized to receive DTG/ABC/3TC FDC who successfully complete 48 weeks of treatment will continue to have access to DTG/ABC/3TC FDC (Continuation Phase) until it is either locally approved and commercially available, the patient no longer derives clinical benefit, the patient meets a protocol-defined reason for discontinuation, or development of DTG/ABC/3TC FDC is terminated. Subjects randomized to the ATV+RTV+ TDF/FTC arm will receive ATV+RTV+TDF/FTC FDC through their Week 48 visit only, after which subjects will complete the study and will need to have alternate arrangements in place to access antiretroviral medication.

Study Completion

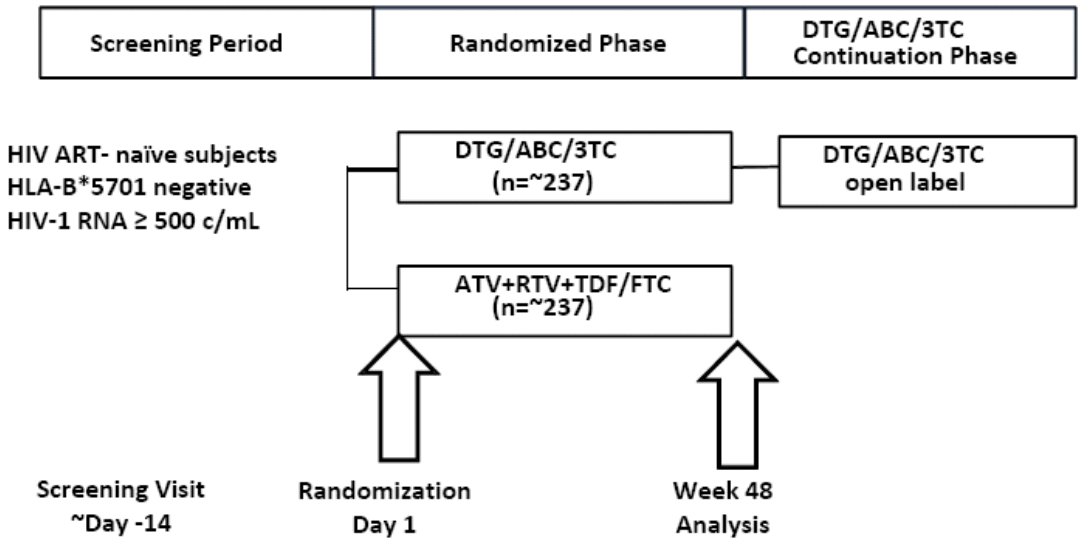
Subjects are considered to have completed the study if they satisfy one of the following:

- Randomized to ATV+RTV+TDF/FTC FDC and completed the Randomized Phase including the Week 48 Study Visit;
- Randomized to DTG/ABC/3TC FDC, completed the Randomized Phase including the Week 48 Visit, and did not enter the Continuation Phase;
- Randomized to DTG/ABC/3TC FDC, completed the Randomized Phase, including the Week 48 study visit, entered and completed the Continuation Phase (defined as remaining on study until commercial supplies of DTG/ABC/3TC become locally available or development of DTG/ABC/3TC is terminated).

Follow Up

Subjects with ongoing AEs or laboratory abnormalities will attend a Follow-up visit approximately four weeks after their last dose of investigational product (DTG/ABC/3TC FDC or ATV+RTV+TDF/FTC FDC). 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, 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 randomized, active-controlled, multicenter, 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 [CDER, 2002].

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

Boosted protease inhibitors such as ATV+RTV are commonly used in women. The use of ATV+RTV as the active comparator in therapy-naïve women is justified based on its indication as an appropriate agent as first line therapy in treatment-naïve HIV-1 infected adults, with specific data in HIV infected pregnant women [Reyataz Package Insert, 2013]. ATV+RTV is recommended as a preferred first-line regimen in the treatment guidelines for women [DHHS, 2013; EACS, 2012; International AIDS Society (IAS), 2010]. With other ART agents, there are concerns with regard to teratogenicity (e.g., efavirenz), drug-drug interactions with oral contraceptives (e.g., Stribild), or efficacy in patients with a viral load greater than 100,000 c/mL (e.g. Complera, a single tablet regimen of rilpivirine, TDF and FTC [Complera Package Insert, 2013]. Boosted PIs

possess a high genetic barrier to resistance, thus are commonly used in subjects at higher risk of virologic failure (e.g. patients with lifestyles or care commitments possibly impairing adherence to dosing schedules).

The open-label design best suits the objectives of this study, and is consistent with other pivotal studies that are included in the prescribing information for boosted protease inhibitors. Blinding of the protease inhibitor component (particularly RTV, with its trademark embossed on the marketed tablet) is a substantial logistical hurdle. ATV-associated hyperbilirubinemia could also lead to unblinding of treatment arms. Moreover, in a double-dummy design, 4 pills per day would have to be administered to all subjects, which is burdensome and does not reflect a real life setting for subjects who may have a single tablet, once daily regimen available as a treatment option. An open-label design may enable assessment of the effect of pill burden upon patient treatment satisfaction, and virological outcome for subjects receiving one versus three pills once per day.

Dual NRTI therapy comprises the backbone of all first line HIV-1 ART according to global treatment guidelines, and both TDF/FTC and ABC/3TC are indicated for use in first line therapy globally.

Given the open-label design, study population and endpoints in this study, an Independent Data Monitoring Committee (IDMC) will not be implemented. The safety of DTG has been assessed in blinded studies during the Phase III program in which an IDMC was utilized and no issues were highlighted necessitating review of this study by an IDMC.

4. SUBJECT SELECTION AND WITHDRAWAL CRITERIA

4.1. Number of Subjects

Sufficient subjects will be screened in order to ensure a total of approximately 474 subjects will be randomized, approximately 237 to each study arm. Subjects will be enrolled from multiple geographic regions.

	Subjects
Screened	~675
Randomized	~474
Completed/Evaluable	~474

4.2. Inclusion Criteria

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK IP 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 jeopardize 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 disqualified Screening genotype which may not be retested).

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, or planned long term work assignments out of the country, etc.).

Laboratory results from the central laboratory services provided by this trial will be used to assess eligibility. If results from central laboratory services (e.g., hematology/ chemistry results) will delay screening beyond the defined 28 day period, use of local laboratory services may be used only after consultation and agreement with GSK.

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

1. HIV-1 infected females (gender at birth) ≥ 18 years of age;

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

   a. is of non-child-bearing potential either defined as 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:

      - Refer to Appendix 6, Section 11.6: Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential.

   Any contraception method must be used consistently, in accordance with the approved product label and for at least 2 weeks after discontinuation of IP. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

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

3. HIV-1 infection as documented by Screening plasma HIV-1 RNA ≥500 c/mL;

4. Documentation that the subject is negative for the HLA-B*5701 allele;

5. Antiretroviral-naïve (≤10 days of prior therapy with any antiretroviral agent following a diagnosis of HIV-1 infection);

6. Signed and dated written informed consent is obtained from the subject or the subject's legal representative prior to screening;

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

4.3. Exclusion Criteria

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

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).

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

Exclusionary medical conditions

1. Women who are pregnant or breastfeeding;
2. Women who plan to become pregnant during the first 48 weeks of the study.
3. Any subject who has had a medical intervention for gender reassignment;
4. Any evidence of an **active** Centers for Disease Control and Prevention (CDC) Category C disease (Section 11.1). Exceptions include cutaneous Kaposi's sarcoma not requiring systemic therapy and historic CD4+ cell counts of <200 cells/mm^3.
5. Subjects with any degree of hepatic impairment;
6. Subjects positive for hepatitis B (+HBsAg) at Screening, or anticipated need for HCV therapy during the study;
7. History or presence of allergy to the study drugs or their components or drugs of their class;
8. Ongoing malignancy other than cutaneous Kaposi's sarcoma, basal cell carcinoma, or resected, non-invasive cutaneous squamous cell carcinoma, or cervical intraepithelial neoplasia; other localized malignancies require agreement between the investigator and the Study medical monitor for inclusion of the subject;

9. Subjects who in the investigator's judgment, poses a significant suicidality risk. Recent history of suicidal behavior and/or suicidal ideation may be considered as evidence of serious suicide risk;
10. History of osteoporosis with fracture or requiring pharmacologic therapy with bisphosphonates (e.g., alendronate, ibandronate, risedronate, zoledronic acid), antiresorptive medications (e.g., denosumab, strontium ranelate, teriparatide), and estrogen receptor modulators (e.g., raloxifene, tamoxifen). Use of calcium and vitamin D is permitted.

Exclusionary Treatments prior to Screening or Day 1

11. Treatment with an HIV-1 immunotherapeutic vaccine within 90 days of Screening;
12. Treatment with any of the following agents within 28 days of Screening: radiation therapy; cytotoxic chemotherapeutic agents; any immunomodulators that alter immune responses (a detailed list is provided in the SPM);
13. Treatment with any agent, except recognized ART as allowed above (Section 4.2), with documented activity against HIV-1 in vitro within 28 days of first dose of IP;
14. Exposure to an experimental drug or experimental vaccine within either 28 days, 5 half-lives of the test agent, or twice the duration of the biological effect of the test agent, whichever is longer, prior to the first dose of IP;
15. **Subjects enrolled in France:** the subject has participated in any study using an investigational drug during the previous 60 days or 5 half-lives, or twice the duration of the biological effect of the experimental drug or vaccine, whichever is longer, prior to screening for the study or the subject will participate simultaneously in another clinical study.

Exclusionary Laboratory Values or Clinical Assessments at Screening

16. Any evidence of primary viral resistance based on the presence of any major resistance-associated mutation [IAS USA, 2013] in the Screening result or, if known, any historical resistance test result. Note: retests of Screening genotypes are not allowed;
17. Any verified Grade 4 laboratory abnormality, with the exception of Grade 4 lipid abnormalities (total cholesterol, triglycerides, High Density Lipoprotein (HDL) cholesterol, Low Density Lipoprotein (LDL) cholesterol). A single repeat test is allowed during the Screening period to verify a result);
18. Any acute laboratory abnormality at Screening, which, in the opinion of the Investigator, would preclude the subject's participation in the study of an investigational compound;
19. Alanine aminotransferase (ALT) ≥ 5 times the upper limit of normal (ULN), or ALT ≥ 3xULN **and** bilirubin ≥ 1.5xULN (with >35% direct bilirubin);
20. Subject has CrCL of <50 mL/min via Cockroft-Gault method;
21. Corrected QT interval (QTc (Bazett)) ≥450msec *or* QTc (Bazett) ≥480msec for subjects with bundle branch block

The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB).

$$QTc\ (Bazett) = \frac{QT}{\sqrt{RR}}$$

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 DTG 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 IPs.

4.5. Withdrawal Criteria

Subjects permanently discontinuing study treatments prior to Week 48 are considered to be withdrawn from the study treatments and also from the study. Similarly, subjects in the DTG/ABC/3TC FDC arm who enter the Continuation Phase but permanently discontinue participation in the Continuation Phase prior to commercially available DTG/ABC/3TC FDC, are considered to be withdrawn from the study treatments 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 <u>may</u> be prematurely discontinued from the study for any of the following reasons:

- Subject or Investigator non-compliance;
- At the request of the subject, Investigator, 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 <u>must</u> be discontinued from the study for any of the following reasons:

- Virologic withdrawal criteria as specified in Section 4.5.1 are met.
- Subject requires substitution or dose modification of DTG, ABC, 3TC, ATV, RTV TDF or FTC;
- 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 as specified in Section 6.4.4.6 and Section 6.4.4.7 are met and no compelling alternate cause is identified;
- Clinically suspected ABC HSR as described in Section 6.4.4.9.
- Rash criteria as described in Section 6.4.4.10 are met and no compelling alternate cause is identified.
- Pregnancy (intrauterine), regardless of termination status of pregnancy. As a reminder, females of reproductive potential who changed their minds and desire to be pregnant, or who state they no longer are willing to comply with the approved pregnancy avoidance methods, should also be withdrawn from the study.

If a 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).

4.5.1. Virologic Criteria for Subject Management and Viral Resistance Testing

Subjects with plasma HIV-1 RNA levels ≥50 c/mL at Week 24 or beyond must have HIV-1 levels re-assessed using the algorithms below (Figure 2 and Figure 3) which detail protocol defined **clinical management** for subjects who either require more careful monitoring (meet "**4 to 6 week HIV-1 RNA testing criterion")** or have met a "**suspected or confirmed virologic withdrawal criterion"**. Investigators should not schedule re-assessment blood draws in the presence of factors that could be associated with virologic blips, such as intercurrent infection, treatment interruption due to toxicity management or non-compliance, or vaccination. Subjects should have received full doses of IP for at least 2 weeks at the time of HIV-1 RNA re-assessment for any HIV-1 RNA level ≥50 c/mL.

Figure 2 Virologic Criteria for Subject Management at Week 24

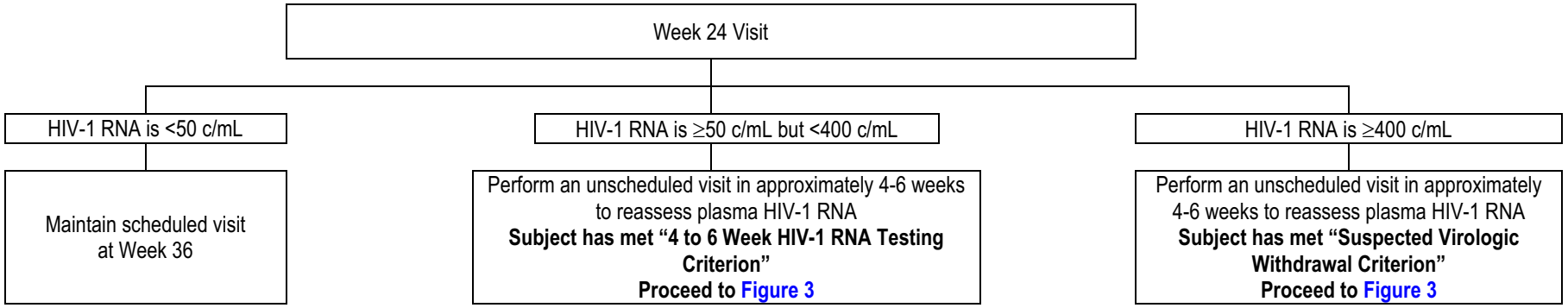
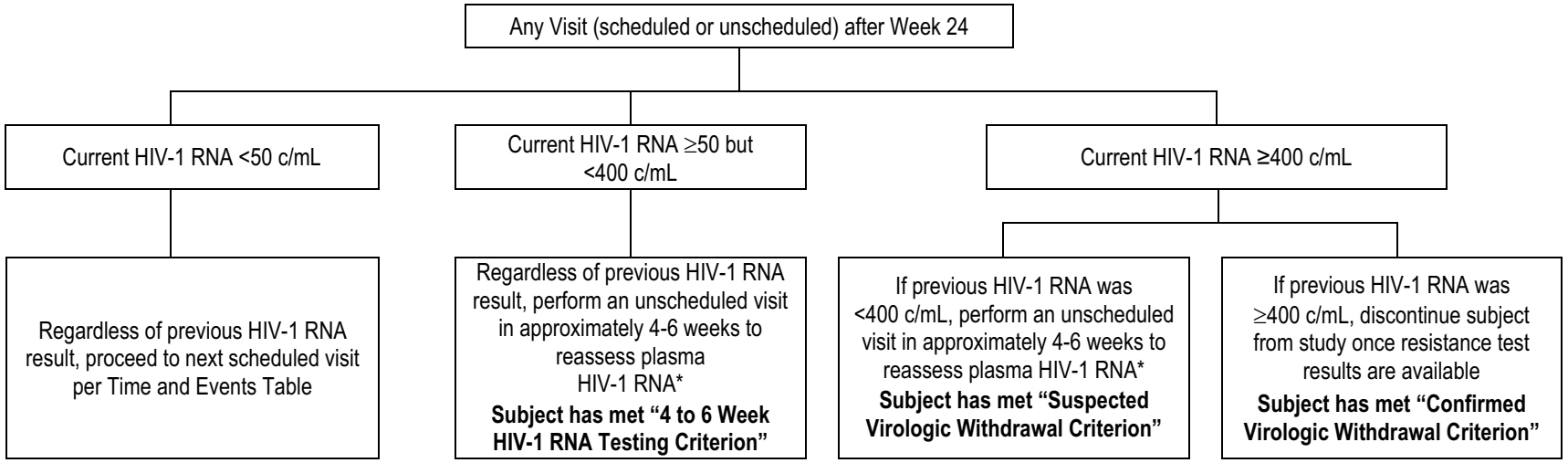


Figure 3 Virologic Criteria for Subject Management after Week 24



*If current visit is Week 48 scheduled visit, perform unscheduled visit in 2-4 weeks rather than 4-6 weeks for assessment of primary endpoint.

If HIV-1 RNA level is ≥400 c/mL on two consecutive assessments, a plasma for storage sample from the "suspected virologic withdrawal criterion" visit will be used for HIV-1 genotype/phenotype testing. Subjects may continue to receive IP at the discretion of the Investigator until results of resistance testing are available at which time the subject must be discontinued from the study. If a subject is prematurely discontinued from the study, the Investigator must make every effort to perform the evaluations outlined in the Time and Events Table (Section 6.1). These data will be recorded as they comprise essential evaluations needed to be done before discharging any subject from the study.

Note: Plasma samples with <400 c/mL of HIV-1 RNA will not be analyzed, as the protease/reverse transcriptase/integrase assays used in this study are not validated for plasma HIV-1 RNA levels <400 c/mL.

4.6. Screening Failures

A subject is considered a screen 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; this 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 disqualified Screening genotype which may not be retested).

Laboratory results from the central laboratory services provided by this trial will be used to assess eligibility. If results from central laboratory services (e.g., chemistry or hematology results) will delay screening beyond the defined 28 day period, use of local laboratory services may be used only after consultation and agreement with GSK.

5. STUDY TREATMENTS

5.1. Investigational Product and Other Study Treatment

IP in this protocol refers to the investigational study drug DTG/ABC/3TC FDC and the comparator drugs ATV, RTV and TDF/FTC FDC. All IP will be supplied by GSK.

Under normal conditions of handling and administration, investigational product 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.

Investigational product must be stored in a secure area under the appropriate physical conditions for the products. Access to and administration of the investigational product will be limited to the investigator and authorized site staff. Investigational product 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/ABC/3TC FDC

DTG/ABC/3TC FDC tablets, 50 mg/600 mg/300 mg are purple, oval, biconvex tablets debossed with '572 Tri' on one side and plain on the other side. The tablets contain 52.6 mg dolutegravir sodium which is equivalent to 50 mg dolutegravir free acid, 702 mg abacavir sulphate which is equivalent to 600 mg abacavir and 300 mg lamivudine. The tablets are packaged into high density polyethylene (HDPE) bottles with child-resistant closures that include induction seals. The bottles contain a desiccant. Tablets **must** be stored in the original package with the bottle tightly closed. Desiccants must be kept in the bottle to protect from moisture.

5.1.2. Tablet Formulations of ATV, RTV, TDF/FTC FDC

Atazanavir (ATV [Reyataz] will be supplied by GSK as commercial product. Each capsule contains 300 mg atazanavir as atazanavir sulphate. Reyataz is manufactured by Bristol Myers Squibb.

Tenofovir disoproxil fumarate/ emtricitabine fixed dose combination (TDF/FTC FDC [Truvada]) will be provided by GSK as commercial product. Each tablet of Truvada contains 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate (which is equivalent to 245 mg of tenofovir disoproxil). Truvada is manufactured by Gilead Sciences.

Ritonavir (RTV [Norvir] will be supplied by GSK as commercial product. Each tablet contains 100 mg ritonavir. Norvir is manufactured by AbbVie Inc.

5.1.3. Dosage and Administration

The study has an open-label design. Details of dosing for both randomized arms are outlined in the following table:

Treatment Arm	Investigational Product	Dose and Dose Interval
DTG/ABC/3TC	**DTG/ABC/3TC FDC**	1 x 50 mg/600 mg/300 mg tablet once daily
ATV+RTV+TDF/FTC	**ATV**	1x 300 mg capsule once daily
	RTV	1 x 100 mg tablet once daily
	TDF/FTC FDC	1 x 300 mg/200 mg tablet once daily

DTG/ABC/3TC FDC may be administered with or without food. ATV+RTV+ TDF/FTC FDC must be taken with food.

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 randomization schedule. Randomization will be conducted via a central randomization procedure following confirmation of fulfillment of study entry criteria. Subjects will be assigned (1:1) to study treatment in accordance with the computer generated randomization schedule. The central randomization schedule, including stratification, will be generated using the GSK validated randomization software RANDALL. Study site personnel will be required to contact the central randomization service for assignment of a unique identifier (designating the subject's randomization 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 Randomized Phase (up to Week 48) and if applicable the Continuation Phase (after Week 48 for subjects randomized to the DTG/ABC/3TC arm).

Subjects who are randomized 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.

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 using pill counts of unused IP. This assessment will be conducted 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 summarized 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 minimize the risk of non-specific increases in the level of HIV-1 plasma RNA at the next scheduled assessment.

DTG/ABC/3TC FDC 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/ABC/3TC FDC can be co-administered with calcium or iron supplements if taken with a meal. Under fasted conditions, DTG/ABC/3TC FDC 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 metformin dose adjustment may be required.

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 that directly affect immune responses are prohibited. HCV therapy during the study will not be permitted as approved HCV therapies at present includes interferon.

Chronic use of systemic (oral or parenteral) glucocorticoids must be avoided; however, short treatment courses (for example, 10 days or less) 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.

5.6.2.1. Prohibited medications for subjects randomized to DTG/ABC/3TC FDC

For subjects randomized to DTG/ABC/3TC FDC, the following medications or their equivalents must not be administered concurrently:

- barbiturates
- carbamazepine
- oxcarbazepine
- phenobarbital
- phenytoin
- St. John's wort
- dofetilide
- rifampin

Dofetilide is prohibited as DTG may inhibit its renal tubular secretion resulting in increased dofetilide concentrations and potential for toxicity.

Methadone - due to potential for decreased plasma concentrations, subjects should be monitored for signs of withdrawal and methadone dose adjusted as appropriate.

5.6.2.2. Prohibited medications for subjects randomized to ATV+RTV + TDF/FTC FDC

For subjects randomized to ATV+RTV+TDF/FTC FDC, the following medications or their equivalents must not be administered concurrently:

- alfuzosin
- rifampin
- irinotecan
- triazolam
- midazolam (oral)
- dihydroergotamine
- ergotamine
- ergonovine
- methylergonovine
- cisapride
- St John's wort
- lovastatin
- simvastatin
- pimozide
- sildenafil

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

5.7. 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 randomized to DTG/ABC/3TC FDC

To provide continued access to unapproved investigational drug to subjects deriving therapeutic benefit, subjects randomized to receive DTG/ABC/3TC FDC and who have successfully completed 48 weeks of treatment in the Randomized Phase will be given the opportunity to continue to receive DTG/ABC/3TC FDC until one of the following occurs:

- DTG/ABC/3TC FDC is locally approved and commercially available,
- The subject no longer derives clinical benefit from receipt of DTG/ABC/3TC FDC,
- The subject meets a protocol-defined reason for discontinuation or
- The development of DTG/ABC/3TC FDC is discontinued.

Subjects randomized to ATV+ RTV + TDF/FTC FDC

As subjects randomized to receive ATV+RTV+TDF/FTC FDC complete the Week 48 visit in the Randomized Phase, they will complete the study. **Investigative sites must make arrangements for provision of ATV, RTV and FTC/TDF FDC** or their individual components **to all subjects early during the study to ensure subject access to medication post study.**

5.8. Treatment of Study Treatment Overdose

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

For the purposes of this study, an overdose is not an AE (Refer to 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 3 Time and Events Table

Procedures	Screen[a]	Day 1	Randomized Phase						Continuation Phase[k]	Withdrawal	Follow-up[l]
			Clinic Visits					Contact at Wk 8 18, 30, 42[r]	Every 12 weeks after Week 48		
			Week 4	Week 12	Week 24	Week 36	Week 48				
Clinical and Other Assessments											
Written informed consent	X										
Inclusion/Exclusion criteria[b]	X	X									
Demography	X										
Prior ART history	X										
Medical history[c]		X									
Current medical conditions		X									
HIV risk factors and mode of transmission		X									
CDC HIV-1 classification	X	X									
HIV associated conditions			X	X	X	X	X		X	X	
Cardiovascular risk assessment[d]		X									
Columbia Suicidality Severity Rating Scale		X[u]	X	X	X	X	X		X	X	
Concomitant medication	X	X	X	X	X	X	X		X	X	X
Limited physical examination[s]	X	X	X	X	X	X	X		X	X	X
12-lead ECG[t]	X										
Adverse events		X	X	X	X	X	X	X	X	X	X
Serious adverse events	X[j]	X	X	X	X	X	X	X	X	X	X
SF-12[w]		X			X		X			X	
HIVTSQ[w]			X	X	X		X			X	

Procedures	Screen[a]	Day 1	Randomized Phase						Continuation Phase[k]	Withdrawal	Follow-up[l]
			Clinic Visits					Contact at Wk 8 18, 30, 42[r]	Every 12 weeks after Week 48		
			Week 4	Week 12	Week 24	Week 36	Week 48				
Confirm understanding of study and management/tolerability of regimen		X	X	X	X	X	X	X	X		
Laboratory Assessments											
Plasma for HIV genotyping	X										
Quantitative plasma HIV-1 RNA	X	X	X	X	X[n]	X[n]	X[n]		X[n]	X	
Lymphocyte subset	X	X	X	X	X	X	X		X	X	X
Plasma for storage[e]	X	X	X	X	X	X	X		X	X	X
HLA-B* 5701 testing[q]	X										
Clinical chemistry	X	X	X	X	X	X	X		X	X	X
Hematology	X	X	X	X	X	X	X		X	X	X
Fasting lipids and glucose[f]		X		X	X	X	X				
Urinalysis and spot urine for protein analysis[g]		X			X		X		X[p]	X[m]	X
Pregnancy test[h]	S	U	S	S	S	S	S		S	S	
HBsAg and hepatitis C antibody	X										
Pharmacogenetic sample[i]		X									
Bone marker analytes (blood)[v]		X			X		X				
Investigational Product											
IVRS	X	X	X	X	X	X	X		X	X	X
Dispense IP		X	X	X	X	X	X[o]		X		
IP accountability (pill counts)			X	X	X	X	X		X	X	

a. The 14-day Screening period maybe extended to 28 days. Randomization may occur as soon as all Screening results are available.
b. 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.
c. Full medical history will be collected. Targeted medical history assessments will include cardiovascular, metabolic (e.g., Type I or II DM), psychiatric (e.g, depression) and renal (e.g., nephrolithiasis, nephropathy, renal failure) disorders.
d. Assessment for cardiovascular risk will include height, weight, blood pressure, smoking history, medical conditions, and family history of premature cardiovascular disease
e. 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, these samples will be used for genotypic and/or phenotypic analyses when subjects meet confirmed virologic withdrawal criteria (see Section 4.5.1).
f. An overnight fast is preferred, however a minimum of a 6 hour fast is acceptable.
g. A morning specimen is preferred.
h. Pregnancy testing. Women of childbearing potential only. S=serum, U=urine. Remind females of reproductive potential of the need to avoid pregnancy while in study and adherence to the study's contraception requirements.
i. 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.
j. Only SAEs related to study participation or to a concomitantly administered GSK product will be collected between obtaining informed consent and administration of IP at Day 1.
k. For subjects who completed randomized DTG/ABC/3TC FDC through Week 48 and entered into DTG/ABC/3TC FDC Continuation Phase: subjects completing the DTG/ABC/3TC FDC Continuation Phase must return to the clinic when transitioning to commercial supplies. Conduct study assessments as specified per the Week 36 schedule at this end of Continuation Phase visit.
l. A Follow up visit may be conducted approximately 4 weeks after the last dose of study provided IP, and is required only if the subject has ongoing AEs or lab abnormalities at the last on study visit. The assessments performed should reflect what is considered medically necessary to assess the event(s).
m. Conduct assessments at Week 48 OR at the Withdrawal visit for subjects who discontinue from the study prior to Week 48, but not both.
n. Beginning at Week 24, subjects with plasma HIV-1 RNA ≥50 but <400 c/mL who elect to remain in study must return every 4-6 weeks for collection of samples for HIV-1 RNA determination and plasma for storage. Genotype and phenotype testing will only be performed with confirmed HIV-1 RNA ≥400 c/mL.
o. For subjects receiving DTG/ABC/3TC FDC in Continuation Phase only
p. Will be tested every 24 weeks (not every 12 weeks)
q. Documentation that the subject had been screened for, and is negative for the HLA-B*5701 allele is acceptable.
r. Contacts at Week 8,18, 30 and 42 are mandatory but may be conducted as a telephone, clinic or home visit (or other type of visit as agreed with GSK).
s. Limited physical examination to include blood pressure at Baseline (recorded in eCRF) for Framingham score assessment, and weight at each visit (recorded in eCRF at Baseline and on lab requisition at all visits) for determination of CrCL. Blood pressure to be measured after resting in a semi-supine position for at least 5 minutes.
t. A 12-lead electrocardiograph (ECG) will be performed after resting in a semi-supine position for at least 5 minutes.
u. On Day 1, the Columbia Suicidality Severity Rating Scale (conducted by voice response system) is to be administered **prior to** randomization.
v. Blood sample for bone marker assessment. Only the result for 25 hydroxy-vitamin D will be reported to the investigator.
w. SF-12 and HIV Treatment Satisfaction Questionnaire **(**HIVTSQ) is recommended to be administered at the beginning of the visit.

6.2. Critical Baseline Assessments

Written informed consent must be obtained from each potentially eligible subject (or his/her legal representative) by study site personnel **prior** to the initiation of any Screening procedures as outlined in this protocol. The consent form must have been approved by the 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.

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 randomized as soon as all Screening assessments are complete and the results are available and documented. All subjects will complete a Screening period of approximately 14 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 28 days to accommodate availability of all Screening assessment results and scheduling. All Screening results must be available prior to randomization.

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.

All subjects must have been screened and be negative for the *HLA-B*5701* allele before randomization can take place. Results must be available for source document verification.

All subjects must provide a plasma sample for determination of primary viral resistance based on the presence of any major resistance-associated mutation.

Subjects who meet all entry criteria are randomized and assigned a randomization number. Subjects not meeting all inclusion and exclusion criteria at initial screen may be re-screened (with the exception of a disqualifying viral phenotype) and receive a new subject number one time. Subjects who are randomized into the trial and subsequently withdrawn from the study for any reason, may not be re-screened.

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 randomization, any changes to the eligibility parameters must be assessed and any results required prior to randomization (e.g. Day 1 urine pregnancy test for women of 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 infected with Hepatitis B (HBV) and/or Hepatitis C (HCV)

Subjects infected with HBV or with an anticipated need for HCV therapy during the study may not be enrolled into this study. Approved HCV therapy currently includes the prohibited medication interferon.

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. CCI [redacted]

Lymphocyte Subsets

Lymphocyte subsets will be collected for assessment by flow cytometry (total lymphocyte counts, percentage and absolute CD4+ lymphocyte counts) according to Time and Events Table (Section 6.1).

HIV Associated Conditions

HIV-associated conditions will be recorded as per Time and Events Table. HIV-associated conditions will be assessed according to the 1993 CDC Revised Classification System for HIV Infection in Adults (Appendix 1, Section 11.1). Indicators of clinical disease progression are defined as:

CDC Category A at enrollment→ Category C event;

CDC Category B at enrollment→ Category C event;

CDC Category C at enrollment→ New Category C Event;

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

6.3.2. Primary Endpoint

The primary endpoint for this study will be the proportion of subjects with plasma HIV-1 RNA <50 copies/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 and <400 c/mL over time;
- Absolute values and change from Baseline in plasma HIV-1 RNA over time;
- Absolute values and changes from Baseline in CD4+ cell counts over time;
- 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 hematology, blood chemistry and fasting lipids (parameters to be tested listed in Table 4 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);
- Periodic assessment of urine/urinalysis parameters as described below;
- 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 will undertake all routine scheduled laboratory evaluations within the study. Refer to the central laboratory manual for specific instructions on sample collection, processing, storage and shipping for each laboratory test.

Table 4 Laboratory Assessments

Hematology	
Platelet Count	Automated WBC Differential:
RBC Count	Neutrophils
WBC Count (absolute)	Lymphocytes
Hemoglobin	Monocytes
Hematocrit	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 Cockcroft-Gault method [Cockroft, 1976].

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) and Hepatitis C (anti-HCV Ab)[a]
Pregnancy test for women of child bearing potential [b]
HLA-B*5701 screening[a]
Urinalysis, urine albumin/creatinine ratio and urine protein/creatinine ratio
Bone marker assessments[c]: bone specific alkaline phosphatase, Procollagen type 1 N-propeptide, Type 1 collagen cross-linked C-telopeptide, osteocalcin, 25 hydroxy-Vitamin D

a. Screening visit only

b. Urine pregnancy test on Day 1; serum pregnancy test at Screening and Weeks 4, 12, 24, 36 and 48 (and at 12 weeks intervals thereafter if applicable).

c. Blood sample for bone marker assessments: since the intention is to utilize these data for research purposes, the Sponsor will not report the results of these assessments to the investigator, except for 25 hydroxy-vitamin D.

6.4.2. Safety Endpoints

- Incidence and severity of AEs and laboratory abnormalities;
- Absolute values and changes over time in laboratory parameters;
- Proportion of subjects who discontinue treatment due to AEs;
- Change from Baseline in fasting lipids and glucose;
- Changes from Baseline in renal and bone markers.

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 2, Section 11.2). 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 minimize the risk of development of resistance.

No toxicity-related dose reductions of IP will be allowed. 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: In the event of a discontinuation of DTG/ABC/3TC FDC for any reason, reinitiation of this drug should be undertaken with caution. The investigator must obtain a complete history of the events surrounding the discontinuation of DTG/ABC/3TC FDC, evaluate for the possibility of a clinically suspected HSR, and initiate subject management as outlined in the DTG IB, regardless of a subject’s *HLA-B*5701* status.

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 6.4.4.4).

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 6.4.4.4). 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.

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 etiology 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 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 stabilization (ALT <5xULN on 2 consecutive evaluations).

When 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 5 and Table 6, 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, stabilize, 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, stabilize or return to within baseline values;

Make every attempt to carry out the **liver event follow up assessments** described below:

- Viral hepatitis serology including:
- Hepatitis A IgM antibody;
- HBsAg and Hepatitis B Core Antibody (IgM);
- Hepatitis C RNA;
- Cytomegalovirus IgM antibody;
- Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
- 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.
- Hepatitis E IgM antibody;
- 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 computerized 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 1.5 x 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. ATV related hyperbilirubinemia

For isolated ≥ Grade 3 unconjugated hyperbilirubinemia attributed to ATV, ATV should be continued unless associated with jaundice or scleral icterus that presents an intolerable cosmetic concern to the subject. For isolated elevations ≥ Grade 3 that cannot be attributed to ATV or to a cause that is not study drug-related, all study medications should be held pending evaluation of etiology.

In the event that an elevation in total bilirubin to ≥2x ULN (>35% direct bilirubin, bilirubin fractionation required) is accompanied by an increase in ALT ≥3x ULN, then the instructions set out in Section 6.4.4.1 must be followed.

6.4.4.4. 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.

6.4.4.5. CPK Elevation

A Grade 3 or higher elevation in CPK should result in a repeat assessment within 2-4 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.

6.4.4.6. Decline in Renal Function

Subjects who experience an increase in creatinine from Baseline of 45 µMol/L (or 0.5 mg/dL) without associated evidence for proteinuria should return for a confirmatory assessment within 2 to 4 weeks. A urinalysis and urine albumin/creatinine ratio 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.

The following criteria are defined based on Cockcroft-Gault estimates of glomerular filtration rate. The criteria are based on recommendations for changes in dosing administration for both DTG/ABC/3TC FDC and TDF/FTC FDC. The DTG IB and current local prescribing information for TDF/FTC FDC should be consulted for additional details on dosing in renally impaired subjects.

Subjects who have a decline in CrCL of >50% must return for a confirmatory assessment as soon as possible. A urinalysis and urine albumin/creatinine ratio should be done at this confirmatory visit. If the estimated CrCL 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., other medications, dehydration, concurrent conditions) should be taken into account, and a nephrology consult may be obtained. 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.

Proximal Renal Tubule Dysfunction (PRTD) is defined as:

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

Subjects meeting criteria for PRTD must return for a confirmatory assessment within 2 weeks. A urinalysis should be done at the time of the confirmatory assessment. If PRTD is confirmed subjects should have IP withheld and the investigator should contact the study medical monitor to discuss the rationale for restarting study drugs (if appropriate). If reinitiation of IP is planned, IP should be withheld for no more than 4 weeks.

6.4.4.7. Proteinuria

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

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

6.4.4.8. 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 DTG/ABC/3TC FDC should be managed in terms of a clinically suspected ABC hypersensitivity, as described below.

6.4.4.9. Abacavir Hypersensitivity Reaction (ABC HSR)

The most significant toxicity associated with ABC is the well-characterized drug-related HSR. A detailed clinical description of this reaction (including the type and severity of events that can occur on re-challenge or reintroduction following ABC interruption for non-HSR reasons) and guidance regarding its management are included in the DTG IB. Investigators must familiarize themselves with this information on ABC HSR in the IB for each of these products prior to initiating subjects on ABC therapy.

Studies have shown that carriage of the *HLA-B*5701* allele is associated with a significantly increased risk of a HSR to ABC. In the prospective study CNA106030 (PREDICT-1), the use of pre-therapy screening for the presence of *HLA-B*5701* and subsequently avoiding ABC in *HLA-B*5701* positive patients, significantly reduced the incidence of clinically suspected ABC HSR from 7.8% (66 of 847) to 3.4% (27 of 803) ($p<0.0001$). In clinical studies EPZ108859 (ARIES) and CNA109586 (ASSERT), 0.8% (4/515) and 3.1% (6/192) of subjects who were *HLA-B*5701* negative and who received ABC developed a clinically suspected ABC HSR, respectively.

In any subject treated with ABC, the clinical diagnosis of suspected HSR (as detailed in the IB) must remain the basis of clinical decision making. Regardless of *HLA-B*5701* status, it is important to permanently discontinue ABC and not re-challenge with ABC (i.e., ZIAGEN™, EPZICOM, KIVEXA, TRIZIVIR™ or DTG/ABC/3TC FDC) if a HSR cannot be ruled out on clinical grounds, due to the potential for a severe or even fatal reaction.

Essential Patient Information

With reference to the IB and the 'Subject Information and Consent Form', Investigators must ensure that subjects are fully informed regarding the following information on the HSR prior to commencing ABC therapy:

- Subjects must be made aware of the possibility of a HSR to abacavir that may result in a life-threatening reaction or death and that the risk of a HSR is increased in individuals who are HLA-B*5701 positive.
- Subjects must also be informed that HLA-B*5701 negative individuals can also experience abacavir HSR. Therefore, ANY subject who develops signs or symptoms consistent with a possible HSR to abacavir MUST CONTACT their doctor IMMEDIATELY.
- Subjects who are hypersensitive to abacavir should be reminded that they must never take any abacavir containing medicinal products (e.g. DTG/ABC/3TC, ZIAGEN, EPZICOM, KIVEXA or TRIZIVIR) again, regardless of their HLA-B*5701 status.
- In order to avoid restarting abacavir, subjects who have experienced a HSR should be asked to return any remaining DTG/ABC/3TC FDC tablets to the Investigator or site staff.

- Subjects who have stopped abacavir for any reason, and particularly due to possible adverse reactions or illness, must be advised to contact their doctor before restarting DTG/ABC/3TC.
- Each subject should be reminded to read the Abacavir Hypersensitivity Warning Card accompanying their study medication and of the importance of keeping it with them at all times.

Reporting of Hypersensitivity Reactions

If a clinically suspected case of HSR to ABC meets one of the International Conference on Harmonization (ICH)-E2A definitions of seriousness listed in Section 6.4.5.2, 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.

6.4.4.10. Skin reactions without other symptoms that are typical of ABC HSR

Including serious skin reactions such as SJS, TEN, Erythema Multiforme or rash with significant liver dysfunction

Subjects should be instructed to contact the Investigator as soon as possible if they develop a rash while on study.

Subjects who develop rash of any grade should be evaluated for the possibility of an ABC HSR or a serious skin reaction such as SJS, TEN or Erythema Multiforme. SJS, TEN and Erythema Multiforme have been reported very rarely in patients taking ABC-containing products. These patients generally do not have the cluster of additional symptoms (e.g., gastrointestinal and respiratory) that characterize the ABC HSR, but they do have features typical of these serious skin reactions.

If a serious skin reaction develops, ABC (and / or all other concurrent medication(s) suspected in the Investigators causality assessment) should be discontinued, and the subject should not be re-challenged with any ABC-containing medicinal product (i.e., DTG/ABC/3TC, ZIAGEN, TRIZIVIR, EPZICOM or KIVEXA).

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

Severe, potentially life-threatening, and fatal skin reactions, including cases of SJS and TEN are listed events in the Local Country Prescribing Information for the first marketed integrase inhibitor, RAL [Isentress US Package Insert, April 2013; Isentress, EU Summary of Product Characteristics, March 2013], and hypersensitivity reactions have been reported with integrase inhibitors, including dolutegravir, and were characterized by rash, constitutional findings, and sometimes, organ dysfunction, including liver injury. For additional information on rash associated with dolutegravir, please see the current version of the DTG IB [GSK Document Number RM2007/00683/11, GSK Document Number 2017N352880_00, GSK Document Number 2017N352880_01].

SJS, erythema multiforme, toxic skin eruptions and drug rash with eosinophilia and systemic symptoms (DRESS) syndrome have also been reported in patients receiving ATV [Reyataz US Package Insert, April 2013; Reyataz EU Summary of Product Characteristics, September 2012].

The following guidance is provided for clinical management of subjects who experience rash alone in the absence of accompanying diagnosis of ABC HSR, systemic or allergic symptoms or signs of mucosal or target lesions.

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 2, Section 11.2).

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

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 unfavorable 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:

Results in death

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.

Requires hospitalization or prolongation of existing hospitalization

> NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for

observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

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

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.

Is a congenital anomaly/birth defect

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

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.

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

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from Baseline, and felt to be clinically significant in the medical and scientific judgment 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.

It is important to note that grading for laboratory abnormalities (See Section 11.2) is an objective assessment conducted at 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 thrombosis
- Deep Venous Thrombosis
- Revascularisation

This information should be recorded 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 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 1, Section 11.1 [CDC, 1993]) 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 behavior). Therefore, it is appropriate to monitor subjects for suicidality before and during treatment. It is recommended that the Investigator consider mental health consultation or referral for subjects who experience signs of suicidal ideation or behavior.

Treatment emergent assessment of suicidality will be monitored during this study using the Columbia Suicide Severity Rating Scale (C-SSRS). The definitions of behavioral suicidal events used in this scale are based on those used in the Columbia Suicide History Form [Oquendo, 2003]. Questions are asked on suicidal behavior, suicidal ideation and intensity of ideation. Day 1 (Baseline) visit questions will be in relation to lifetime experiences and current experiences (within the past 2 months) and all subsequent questioning in relation to the last assessment. The C-SSRS is to be administered using an interactive voice response system 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 adverse event while participating in this study. This may include, but is not limited to, an event that involves suicidal ideation, a preparatory act toward imminent suicidal behavior, a suicide attempt, or a completed suicide. The investigator will exercise his or her medical and scientific judgment in deciding whether an event is possibly suicide-related. PSRAE forms should be completed and reported to GSK within one week of the investigator diagnosing a possible suicidality-related adverse event.

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 IP re-administration, when administration is disrupted for more than 7 days (e.g. temporary interruption of IP).

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 5 and Table 6 once the investigator determines that the event meets the protocol definition for that event.

Table 5 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 plus Bilirubin≥2xULN (35% direct)	24 hours[1]	SAE data collection tool Liver Event CRF and liver imaging and/or biopsy CRFs if applicable	24 hours	Updated SAE data collection tool Updated Liver Event CRF[2]

Table 6 Other Events Requiring Prompt Reporting

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
Pregnancy	2 Weeks	Pregnancy Notification Form	2 Weeks	Pregnancy Follow up Form
Suspected ABC HSR	1 Week	ABC HSR CRF[3]	1 Week	Updated ABC HSR CRF[3]
ALT≥5xULN that persists ≥2 weeks	24 hours[1]	Liver Event CRF[2]	24 hours	Updated Liver Event CRF[2]
ALT ≥8xULN	24 hours[1]	Liver Event CRF[2]	24 hours	Updated Liver Event CRF[2]
ALT ≥3xULN or ALT ≥3 fold increase from baseline value with appearance or worsening of symptoms of hepatitis or hypersensitivity	24 hours[1]	Liver Event CRF[2]	24 hours	Updated Liver Event CRF[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.
3. ABC HSR CRF required only if event meets one of the ICH-E2A definitions of seriousness'.

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.

Procedures for documenting, transmitting and follow-up of medical device incidents along with the regulatory reporting requirements for medical devices 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, IRB/ 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 4], must be performed by the central laboratory, Quest Diagnostics. Laboratory assessments must be conducted in accordance with the Central Laboratory Manual and Protocol Time and Events Table. Laboratory requisition forms must be completed and samples must be clearly labeled 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 additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in patient management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the subject's CRF. Refer to the SPM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

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.

Health Related Quality of Life (HRQoL) will be assessed by the SF-12 (12-Item Short Form Health Survey) which was derived from the 36-Item Short Form Health Survey (SF-36) and has been shown to provide adequate mental component summary (MCS) and well as physical component summary (PCS) scores [Ware, 1996]. The SF-12 has been studied in the HIV population and can discriminate between patients by HIV disease severity as measured by CD4+ cell count and HIV-1 viral load. The SF-12 will be administered as a paper questionnaire.

HIVTSQ: The HIV treatment satisfaction questionnaire (status version) [Woodcock , 2001; Woodcock, 2006] is a 10-item self-reported scale that measures overall satisfaction with treatment and by specific domains e.g. convenience, flexibility. The HIVTSQ will be administered as a paper questionnaire.

6.5.1. Health Outcomes Endpoints

- Change from Baseline in health related quality of life using SF-12 at Week 48.

- Treatment satisfaction for subjects treated with DTG/ABC/3TC FDC once daily and those treated with ATV+RTV+TDF/FTC FDC once daily at weeks 4, 12, 24, and 48 (or withdrawal from the study).

6.6. Viral Genotyping and Phenotyping

Whole venous blood samples will be obtained from each subject to provide 'plasma for storage samples' according to the Time and Events Schedule in Section 6.1 (for potential viral genotypic and phenotypic analyses ('Plasma for storage' samples).

Details concerning the handling, labeling and shipping of these samples will be supplied separately. Genotypic and phenotypic analyses may be carried out by Monogram Biosciences using, but not limited to, their Standard Phenosense and GenoSure testing methods for protease (PRO) and reverse transcriptase (RT) and Integrase assays.

For Screening virologic evaluations, only viral genotype will be analyzed and this will be performed through Quest Diagnostics.

6.6.1. Virology Endpoints

- Incidence of treatment-emergent genotypic and phenotypic resistance in subjects who meet confirmed virologic withdrawal criteria.

6.6.2. HIV-1 Polymerase Viral Genotyping and Phenotyping

At Screening, samples will be collected for HIV-1 polymerase (pol) genotype using a Quest Diagnostics genotype assay and results will be provided to the Investigator to assist in the determination of subject eligibility (Section 4.3).

Subjects meeting 'confirmed virologic withdrawal criterion' 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 'suspected virologic withdrawal criterion' (additional subsequent samples may be analyzed); these results will be reported to the Investigator as soon as available to provide guidance for election of an alternative regimen.

6.7. Pharmacogenetic Research

Information regarding PGx research is included in Appendix 3 (Section 11.3).

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 3, Section 11.3). 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 the DTG/ABC/3TC FDC administered once daily is non-inferior to once daily ATV+RTV+TDF/FTC FDC.

Non-inferiority can be concluded if the lower bound of a two-sided 95% confidence interval for the difference in response rates between the two treatment arms is greater than -12%. If r_d is the response rate on DTG/ABC/3TC FDC and r_a is the response rate on ATV+RTV+TDF/FTC FDC 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

A non-inferiority margin is set as 12% in this study. The rationale is shown in Table 7. The endpoint for the primary comparison is response rate, i.e. the proportion of subjects with plasma HIV-1 RNA below 50 c/mL at Week 48. Table 7 shows the response rates from studies of dual-NRTI therapy and dual-NRTI + third agent therapy. Though time points are different among the studies, the differences of response rates between dual-NRTI therapy and dual-NRTI + third agent are similar. These differences in response rates range from 34% to 49% and all of the lower bounds of 95% confidence interval are no less than 0%, which shows that the additional effect of third agent therapy in each study is statistically significant. Moreover, the pooled difference (the 95% confidence interval) of these response rates is 39% (33%, 45%). A non-inferiority margin of 12% is small enough compared to the additional effect of third agent therapy, because the non-inferiority margin is much less than the half of the lower bound of 95% confidence interval for the pooled difference.

Also the non-inferiority margin of 12% is in the mid-range of the margins described in a review of non-inferiority trials in HIV conducted between 2000 and 2007, where the margins vary between 10% and 15% [Hill, 2008]. This suggests further that a non-inferiority margin of 12% is reasonable.

Table 7 The proportion of subjects with plasma HIV-1 RNA below 50 c/ml of dual-NRTI therapy and dual NRTI + third agent therapy

Study Number	N	Endpoint	Timepoint	Dual-NRTI Therapy	Dual-NRTI Therapy + Third Agent	Difference[a] (95% CI)
				Response Rate	Response Rate	
PROAB3001	232	<50 c/ml	Week 48	ZDV+3TC 1%(1/116)	ZDV+3TC+APV 34%(40/116)	34% (20.7%, 45.7%)
CNAAB3003	173	<50 c/ml	Week 48	ZDV+3TC 3%(3/86)	ZDV+3TC+ABC 44%(38/87)	40% (26.2%, 53.3%)
AVANTI-2	103	<50 c/ml	Week 52	ZDV+3TC(n=51) 6%	ZDV+3TC+IDV(n=52) 48%	42% (24.2%, 58.8%)
AVANTI-3	105	<50 c/ml	Week 28	ZDV+3TC(n=52) 10%	ZDV+3TC+NFV(n=53) 58%	49% (31.7%, 64.7%)

a. Defined as the difference of response rate calculated by (dual-NRTI + third agent) - (dual-NRTI therapy)

Response Rate assumptions

In previous DTG and ATV/RTV studies, response rates in women have consistently been lower than those seen in men. Results of DTG studies can be found in the most current version of the IB.

In the SINGLE study (ING114467) comparing DTG+ABC/3TC once daily to Atripla once daily in treatment naive subjects, the overall response rate <50 c/ml (ITT-E, Snapshot) at Week 48 for the DTG arm was 88% (364/414) with a 85% (57/67) response rate in women compared to 88% (307/347) in men. In the SPRING-2 study (ING113086) comparing DTG once daily to RAL BID both in combination with a fixed dose dual NRTI treatment, the overall response rate <50 c/ml (ITT-E, Snapshot) at Week 48 for the DTG arm was 88% (361/411) with a 84% (53/63) response rate in women compared to 89% (308/348) in men.

In the CASTLE study [Molina, 2008] comparing ATV+RTV+FTC once daily to LPV/RTV +FTC once daily in treatment naive subjects, the overall response rate <50c/ml (ITT, non completers = failure) was 78% (343/440) at Week 48 in the ATV/RTV arm. Gender differences in response rates were published for the Week 96 analysis [Squires, 2011] where the overall response rate <50 c/ml (ITT, non completers=failure) was 74% (327/440) with a 67% (93/138) response rate in women compared to 77% (234/302) in men.

A recent study [DeJesus, 2012] comparing ATV+RTV+FTC/TDF to Stribild (ELV/COBI/TDF/FTC) in HIV-1 infected ART naive subjects reported an overall response rate of 87% (308/355) <50 c/ml (ITT, Snapshot). The corresponding response rate in women was 82% (32/39) compared to 87% (276/316) in men. However, with so few subjects included in the study, the estimate of the response rate in women is not robust.

The response rates for the four studies are shown together in Table 8.

Table 8 The proportion of subjects with plasma HIV-1 RNA below 50 c/ml

	DTG Response Rates		ATV/RTV Response Rates		
	SINGLE[a] Week 48	SPRING-2[a] Week 48	CASTLE[b] Week 48	CASTLE[b] Week 96	DeJesus[a] Week 48
All	88%	80%	78%	74%	87%
Men	88%	89%	-	77%	87%
Women	85%	84%	-	67%	82%

a – ITT-E Snapshot
b – ITT, non completers=failure

The discontinuation rates observed in women across HIV studies are higher than those observed in men and vary between studies. With a Snapshot analysis, subjects who discontinue from the study are considered to be non-responders at subsequent visits and as such can have a substantial impact on the response rates observed.

The overall discontinuation rates for women compared with men were 23% (30/130) versus 15% (105/703), and 18% (22/119) versus 11% (81/703) in the Week 48 analyses from SINGLE and SPRING-2 studies, respectively. In the Week 48 analysis of the CASTLE study, the overall discontinuation rate was 12% (53/440). The gender

differences published for the Week 96 analysis show a higher rate in women of 22% (31/138) compared to 15% (45/302) in men. One of the few studies specifically designed to look at the outcomes by gender, the GRACE study [Currier, 2010] using darunavir+RTV, reported a discontinuation rate of 33% (94/287) in women compared to 23% (33/142) in men. However, it should be noted that this study was in treatment-experienced patients. The number of female subjects in these studies, with the exception of the GRACE study, was relatively small and as such the estimates of response rates will not be as robust as those overall or for men. There has also been a wide range of discontinuation rates observed with a clear signal that the rates in women are higher than in men. It may be possible to reduce the number of avoidable discontinuations through careful and well thought out study design and management but it is likely that a higher rate of discontinuation will be seen in this study than in previous mixed gender DTG studies.

The discontinuation rates for these four studies are shown together in Table 9.

Table 9 Premature Discontinuation Rates

	DTG Discontinuation Rates		ATV/RTV Discontinuation Rates		
	SINGLE Week 48	SPRING-2 Week 48	CASTLE Week 48	CASTLE Week 96	GRACE Week 48
All	16%	13%	12%	17%	30%
Men	15%	11%	-	15%	23%
Women	23%	18%	-	22%	33%

The primary efficacy endpoint will be the proportion of subjects achieving <50 c/ml in HIV-1 RNA at Week 48 using a Snapshot analysis and an ITT-E population. Therefore, assuming an 80% response rate in both arms with a 12 % non-inferiority margin and a 2.5% level of significance, a sample size of 237 subjects per arm would provide 90% power.

8.2.2. Sample Size Sensitivity

Table 10 shows the sensitivity of the sample size and the power to the assumptions used in its calculation. The table shows that the planned sample size still provides at least 85% power if the assumptions of 80% response rate per arm vary as indicated.

Table 10 Calculation of sample size and power based on assumptions for response rates

Week 48 Response Rate DTG vs. ATV	Sample Size per arm (based on 90% power)	Power (based on 237 subjects per arm)
85% vs. 85%	194	95%
80% vs. 75%	129	99%
80% vs. 80%	**237**	**90%**
75% vs. 70%	146	99%
75% vs. 75%	275	85%

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 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

This population will consist of all randomized subjects. Subjects will be assessed according to their randomized treatment even if no study treatment was taken or the wrong treatment was received.

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 in certain scenarios. However, since changes in ART are not permitted in this protocol, all such subjects who change ART will be considered non-responders. 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 timepoint 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.

A last observation carried forward (LOCF) dataset in which missing values will be carried forward from previous, non-missing available on treatment assessments will be used in the analysis of health outcomes data. Further details will be provided 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/ABC/3TC FDC will be declared non-inferior to treatment with ATV+RTV+TDF/FTC FDC if the lower end of a two-sided 95% confidence interval for the difference between the two groups in response rates at Week 48 lies above -12%.

8.3.3.2. Other Comparisons of Interest

The analysis described above will also be performed using the PP population and the results will be compared for consistency with the results from the ITT-E population. If both analyses show non-inferiority then the hypothesis that the antiviral effect of treatment with DTG/ABC/3TC FDC is superior to treatment with ATV+RTV+TDF/FTC FDC will also be tested in the ITT-E population at the two-sided 5% level of significance. Superiority will be declared if the lower end of the 95% confidence interval calculated in the ITT-E analysis 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.

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 48 visit. Further data cuts and analyses may be conducted as necessary in order to support regulatory submissions and publications.

8.3.5. Key Elements of Analysis Plan

The study design is open-label however the central GSK team responsible for the conduct and analysis of the study will not review any summaries of data grouped by treatment prior to database freeze for the primary Week 48 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, four 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) and Baseline CD4+ cell count (≤ vs. >350 cells/mm^3).
The CMH estimate of the common difference in rates across strata will be calculated as the weighted average of the strata-specific estimates of the difference in response rates between the two arms as follows:

- If nk is the number of DTG/ABC/3TC FDC treated subjects, mk is the number of ATV+RTV+TDF/FTC FDC treated subjects, and Nk = nk + mk is the total number of subjects in the kth 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, 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.

Secondary analyses of plasma HIV-1 RNA and CD4+ cell count will be analyzed over time using the OC analysis dataset. The proportion of subjects with HIV-1 RNA below 50/400 copies/ml over time will be presented using both the Snapshot and OC datasets. The incidence of HIV-1 disease progression (AIDS and death) will be presented. Further details of secondary efficacy analyses will be included 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 summarized by treatment group. The proportion of subjects reporting AEs will be tabulated for each treatment group. The following summaries of AEs will be provided:

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

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

Renal markers and bone markers will be summarized by visit and treatment group based on an OC dataset. Cardiovascular risk based on Framingham score will be summarized at Baseline based on an OC dataset.

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

8.3.5.3. Health Outcomes Analyses

The SF-12 includes one scale measuring each of 8 health domains: physical functioning, role participation with physical health problems (role physical), bodily pain, general health, vitality, social functioning, role participation with emotional health problems and mental health, with two factors for health status: one for physical component summary (PCS) and mental component summary (MCS).

Changes from Baseline in scores for PCS and the MCS will be compared between the two treatment arms at each time point. Exploratory analysis will be done to assess which aspects of health are most impacted at the item level and health domain level.

The HIVTSQ was developed to evaluate treatments for HIV and patient satisfaction. 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.

The HIVTSQ items are summed up to produce a treatment satisfaction score (0 to 60) and an individual satisfaction rating for each item (0 to 6) and two subscales: general satisfaction/clinical and lifestyle/ease subscales. These scores will be summarized 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, protease inhibitors, and INIs will be summarized by treatment arm. Details of the analyses to be performed will be specified in the RAP.

8.3.5.5. Pharmacogenetic Analyses

See Appendix 3 (Section 11.3) 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 favorable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH 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:

- IRB/IEC review and favorable 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 3, Section 11.3, 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 CSR. 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.

10. REFERENCES

Atripla Product Information, April 2013

Centers for Disease Control and Prevention (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.

Cockroft DW, Gault MH. Pediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31-41.

Complera US Product Information, January, 2013

Cooper DA, Steigbigel RT, Gatell JM, et al. Subgroup and resistance analyses of raltegravir for resistant HIV-1 Infection. *N Engl J Med.* 2008;359:355-65.

Currier J, Averitt Bridge D, Hagins D. Sex-Based Outcomes of Darunavir–Ritonavir Therapy: The GRACE (Gender, Race, and Clinical Experience) Study; Ann Intern Med. 2010; 153(6): 349–357. doi: 10.1059/0003-4819-153-6-201009210-00002

DeJesus E, Rockstroh JK, Henry K, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate versus ritonavir-boosted atazanavir plus co-formulated emtricitabine and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: a randomized, double-blind, phase 3, non-inferiority trial. *Lancet* 2012;379(9835):2429–2438.

Department of Health and Human Services (US DHHS) Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for Industry. Antiretroviral Drugs Using Plasma HIV RNA Measurements - Clinical Considerations for Accelerated and Traditional Approval. October 2002

Department of Health and Human Services (US DHHS). Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Updated February 12, 2013. Available at http://www.aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf.

European AIDS Clinical Society (EACS) Guidelines for the clinical management and treatment of HIV Infected Adults in Europe, 2012. Available at http://www.europeanaidsclinicalsociety.org/images/stories/EACS-Pdf/EacsGuidelines-v6.1-2edition.pdf.

Fleiss J.L. *Statistical Methods for Rates and Proportions.* 2 ed. New York:John Wiley; 1981.

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.

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

Hazuda DJ, Miller MD, Nguyen BY and Zhao J. Resistance to the HIV-integrase inhibitor raltegravir: Analysis of Protocol 005, a Phase II study in patients with triple-class resistant HIV-1 infection. Abstract 8, XVI International HIV Drug Resistance Workshop. *Antiviral Therapy.* 2007a;12:510.

Hill, A, Sabin, C. Designing and interpreting noninferiority trials in naïve and experienced patients. AIDS. 2008;22(8):913-921.

International AIDS Society (IAS)–USA Antiretroviral Treatment of Adult HIV Infection: 2010 Recommendations of the International AIDS Society-USA Panel. Thompson et al. *JAMA.* 2012;308(4):387-402.

International AIDS Society (IAS)–USA. Update of the Drug Resistant Mutations in HIV-1: March 2013. Topics in HIV Medicine 2013;21(1): 6-14.

Isentress EU Summary of Product Characteristics, March 2013

Isentress US Product Information, April 2013;

Lennox JL, DeJesus E, Berger DS, et al. Raltegravir Versus Efavirenz Regimens in Treatment-Naive HIV-1–Infected Patients: 96-Week Efficacy, Durability, Subgroup, Safety, and Metabolic Analyses. *J Acquir Immune Defic Syndr* 2010;55(1):39-48.

Lui K.-J., Kelly C. A Revisit on Tests for Homogeneity of the Risk Difference. *Biometrics.* 2000;56:309-315.

McColl DJ, Fransen S, Gupta S, et al. Resistance and cross-resistance to first generation integrase inhibitors: Insights from a Phase II study of elvitegravir (GS-9137). Abstract 9, XVI International HIV Drug Resistance Workshop. *Antiviral Therapy.* 2007;12:S11.

Molina J, LaMarca A, Andrade-Villanueva J, et al. Efficacy and safety of once daily elvitegravir versus twice daily raltegravir in treatment-experienced patients with HIV-1 receiving a ritonavir-boosted protease inhibitor: randomised, double-blind, phase 3, non-inferiority study. *Lancet Infect Dis* 2012;12: 27–35.

Molina JM, Andrade-Villanueva J, Echevarria J, et al. Once-daily atazanavir/Ritonavir versus twice-daily lopinavir/Ritonavir, each in combination with tenofovir and Emtricitabine, for management of antiretroviral-naïve HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. Lancet. 2008; 372; 646-655.

Oquendo MA, Mann J. Risk Factors for suicidal behaviour : utility and limitations of research instruments (2003). In M.B. First [Ed] Standardized Evaluation in Clinical Practice, pp 103- 130.

Paterson D, Swindells S, Mohr J, et. al. How Much Adherence is Enough? A Prospective Study of Adherence to Protease Inhibitor Therapy Using MEMSCaps. Abstract 92, 6th Conference on Retrovirus and Opportunistic Infections. 1999; 84.

Reyataz EU Summary of Product Characteristics, September 2012.

Reyataz US Product Information, April 2013.

Sato T. On the variance estimator for the Mantel-Haenszel risk difference. *Biometrics.* 1989;45:1323-1324.

Sax PE, DeJesus E, Mills A, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: a randomised, double-blind, Phase 3 trial, analysis of results after 48 weeks. *Lancet* 2012;379 (9835):2439–2448.

Squires KE, Johnson M, Yang R, et al. Comparative gender analysis of the efficacy and safety of atazanavir/ritonavir and lopinavir/ritonavir at 96 weeks in the CASTLE study. J Antimicrob Chemother. 2011; 66: 363-370.

Stribild, Product Information, 2012

Truvada, Product Information, July 2012

Ware JE, Kosinski M, and Keller SD. A 12-Item Short-Form Health Survey: Construction of scales and preliminary tests of reliability and validity. Medical Care, 1996;34(3):220-233.

Woodcock A, Bradley C (2001). Validation of the HIV Treatment Satisfaction Questionnaire (HIVTSQ). *Quality of Life Research. 10*:517-531.

Woodcock A, Bradley C (2006). Validation of the Revised 10-item HIV Treatment Satisfaction Questionnaire Status Version and New Change Version . *Value in Health. 9*:320-333.

11. APPENDICES

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

Reference - 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.

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

11.2. Appendix 2: 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 utilized 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
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)]

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

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

CLINICAL					
PARAMETER		**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
	Pediatric ≤ 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 ≤ 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
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

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

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

CLINICAL				
PARAMETER	**GRADE 1 MILD**	**GRADE 2 MODERATE**	**GRADE 3 SEVERE**	**GRADE 4 POTENTIALLY LIFE-THREATENING**
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.
   Basic Self-care Functions – Young Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implement).
   Usual Social & Functional Activities – Adult: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.
   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).

11.3. Appendix 3: 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 medicines used in this study
- Relationship between genetic variants and safety and/or tolerability of DTG or other medicines used in this study
- Relationship between genetic variants and efficacy of DTG or other 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 randomized 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 utilize 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 summarize 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.

11.4. 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 favorable benefit: risk and no alternative medicine available (Table 11, Figure 4)
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 12, Figure 5).

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:

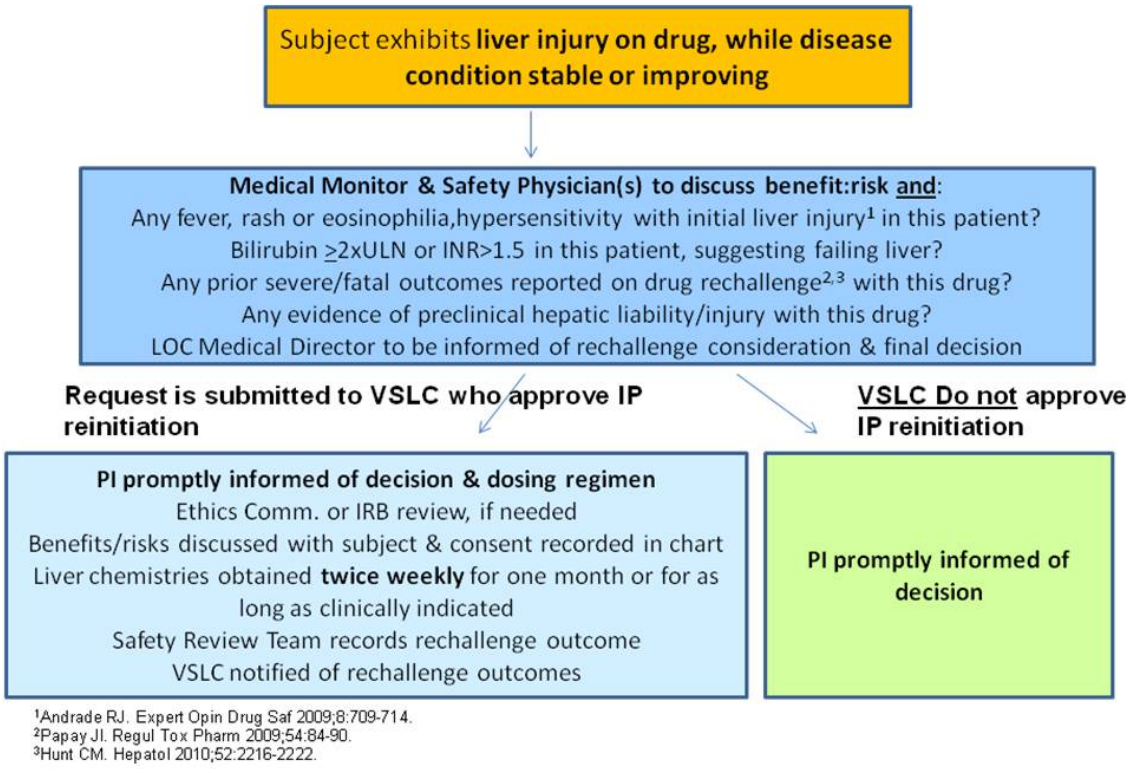
- hypersensitivity with initial liver injury (e.g. fever, rash, eosinophilia) [Andrade, 2009]
- jaundice or bilirubin≥2xULN with initial liver injury
- prior serious adverse event or fatality has earlier been observed with drug rechallenge [Papay, 2009; Hunt, 2010]
- evidence of drug-related preclinical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

VSLC Decision Process for Drug Rechallenge Approval or Disapproval (Figure 4)

- 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 11**)**.

- 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 INR≥1.5
    - 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 (GSK) or Clinical Lead and Medical and Development Group Lead (Pfizer).
  - Request is taken to full VSLC for final decision

Figure 4 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 11 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 is drug held while labs and evaluation is completed to assess diagnosis.

VSLC Decision Process for Drug Restart Approval or Disapproval (Figure 5):

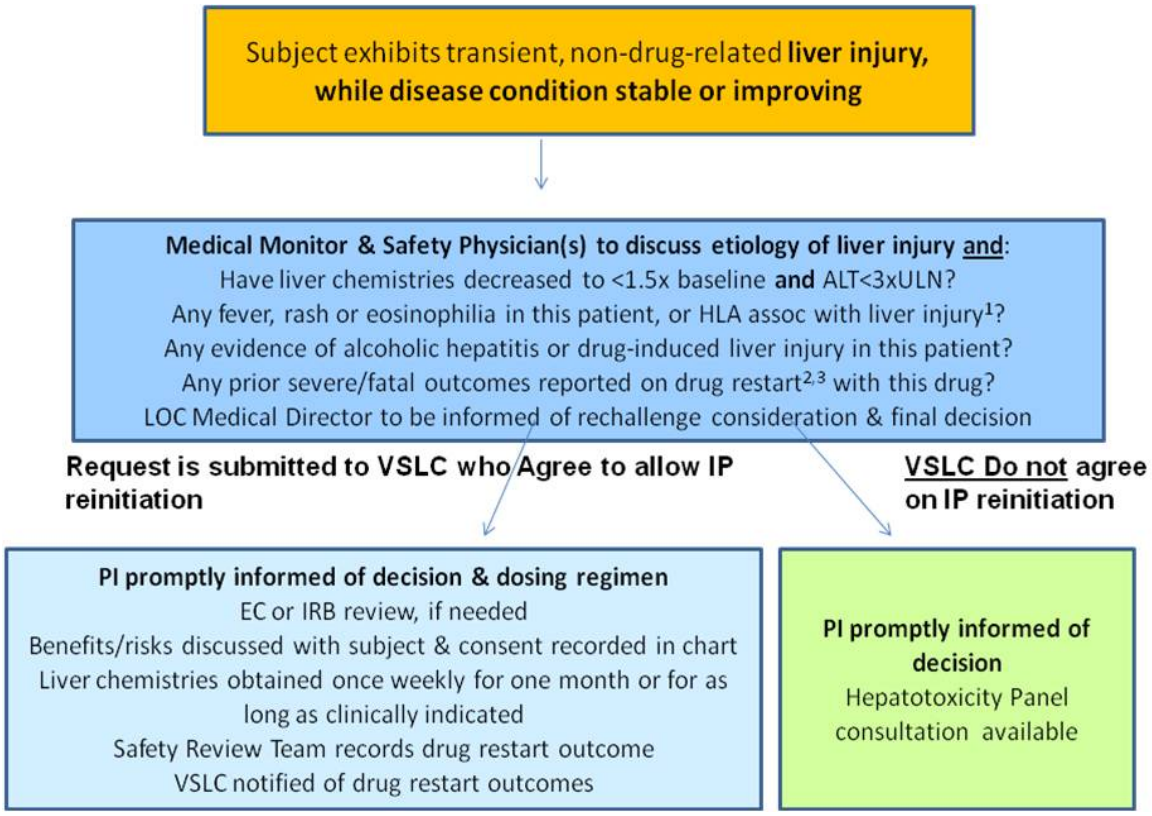
- PI requests consideration of drug re-initiation for a subject stable or improving on IP, who exhibits liver chemistry elevation meeting subject stopping criteria, which is transient, non-drug-related, and liver chemistries improve to within 1.5x baseline and ALT< 3xULN.
- GSK Medical Monitor and Clinical Safety Physician to review the subject's diagnosis, restart risk factors and complete checklist (Table 12).
  - ***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 12 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 (GSK) or Clinical Lead and Medical and Development Group Lead (Pfizer).
- 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 5 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:

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

References:

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

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

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

11.5. Appendix 5: Country Specific Requirements

United Kingdom

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

Study Duration

In this study, the date of last study treatment administration in the UK will be determined by the completion of the 48 week randomized phase of the study for the last UK subject enrolled (it will not be determined by the completion of the Continuation Phase). The last subject will be enrolled by February 2015, and hence the last study treatment administration will occur by 28 February 2016.

(Note: The Continuation Phase is intended to provide subjects on DTG/ABC/3TC FDC with post-study access to DTG/ABC/3TC FDC until it becomes available in their countries. For subjects in the UK, the Continuation Phase is anticipated to conclude by 31 March 2015, when DTG/ABC/3TC FDC is anticipated to become available).

11.6. Appendix 6: Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

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

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

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

Reference

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

11.7. Appendix 7: Protocol Changes

11.7.1. Protocol Amendment 01 (12-AUG-2013)

This protocol amendment applies to all participating sites.

Rationale for Protocol Amendment 01:

i. For clarification purposes, the Child-Pugh Classification has been removed as a method to determine the degree of hepatic impairment (Exclusion Criterion Number 5). Of note, there is no change to the intended study population as a result of this change (i.e. subjects with any degree of hepatic impairment are still excluded). The Child-Pugh Classification is intended to grade hepatic impairment in subjects already known to have hepatic impairment. Application of this tool to subjects with no hepatic impairment will result in a score of at least 5 and a classification of 'mild hepatic impairment', therefore it is not a suitable screening tool for populations which include those with no hepatic impairment.

ii. For clarification purposes, Figure 2, in Section 4.5.1. Virologic Criteria for Subject Management at Week 24, has been updated to differentiate between the two scenarios in which re-testing for HIV-1 RNA levels is required and to match central laboratory wording to be provided to sites when subjects meet virologic management criteria. Of note, the amendment does not result in any change in action for sites.

iii. Removal of the assessment for bone marker analytes during the Continuation Phase (every 12 weeks after Week 48): This requirement was included in the Time and Events Schedule in error. Subjects on the ATV+RTV+TDF/FTC arm will have completed the study at Week 48 and monitoring of bone marker analytes for subjects on the DTG/ABC/3TC arm beyond Week 48 is not considered necessary. Since this assessment is not part of a primary or key safety endpoint, the removal of this assessment at this timepoint was previously documented in a Study File Note and is now included in this protocol amendment for completeness.

iv. Inclusion of a reference omitted in the original protocol [IAS USA, 2013].

v. For clarification purposes, corrections have been made to formatting issues and typographical errors and to maintain consistency in use of wording and terms between sections.

- The term 'virologic failure' has been replaced with 'confirmed virologic withdrawal criteria' to maintain consistency with wording for virologic criteria for subject management in Section 4.5.1.

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

Protocol Summary, Secondary Objectives, bullet 3

The following text has been revised:

- To assess the development of viral resistance in subjects ~~experiencing virologic failure~~ **who meet confirmed virologic withdrawal criteria**;

Protocol Summary, Study Endpoints/Assessments, paragraph 5

The following text has been revised:

Virology endpoints will include the incidence of treatment emergent genotypic and phenotypic resistance in subjects ~~experiencing virologic failure~~ **who meet confirmed virologic withdrawal criteria**.

2. Objectives, Secondary Objectives, bullet 3

The following text has been revised:

To assess the development of viral resistance in subjects ~~experiencing virologic failure~~ **who meet confirmed virologic withdrawal criteria**

4.3. Exclusion Criteria

The following text has been revised:

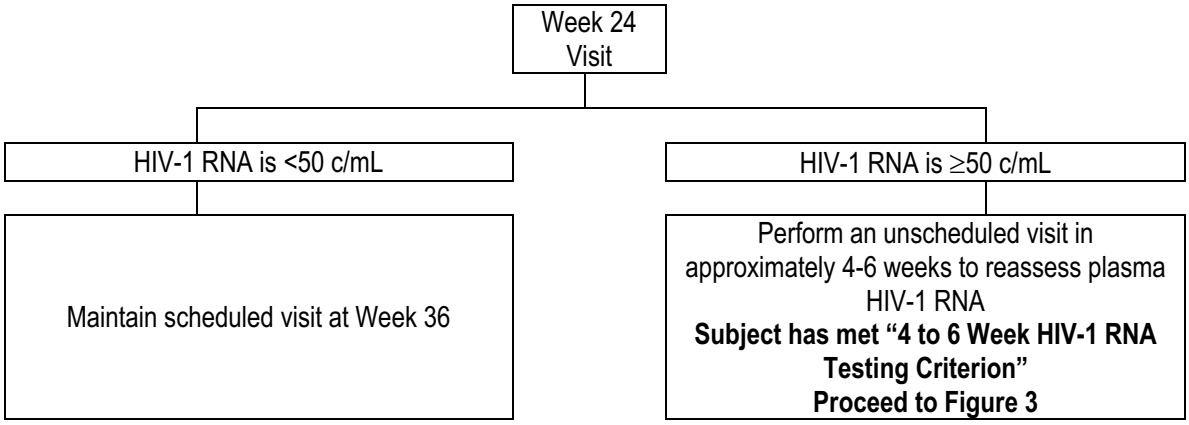
5. Subjects with any degree of hepatic impairment~~, (Class A or greater) as determined by Child-Pugh classification (Section 11.2). For subjects requiring anticoagulation therapy, discussion with the study medical monitor will be required~~;

16. Any evidence of primary viral resistance based on the presence of any major resistance-associated mutation [IAS USA, 201~~2~~**3**] in the Screening result or, if known, any historical resistance test result. Note: retests of Screening genotypes are not allowed;

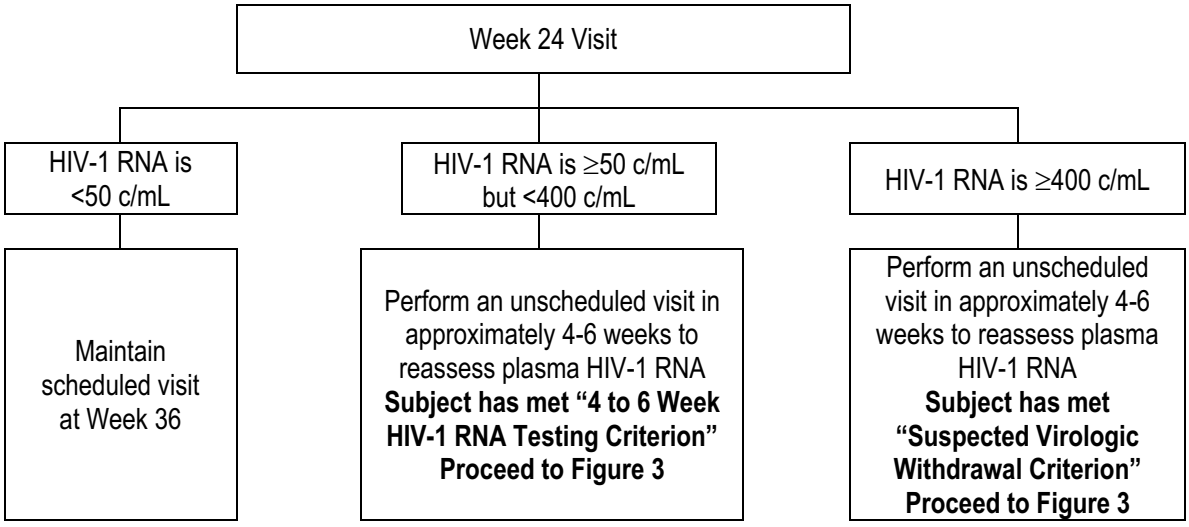
4.5.1. Virologic Criteria for Subject Management and Viral Resistance Testing, Figure 2. Virologic Criteria for Subject Management at Week 24

The following Figure has been revised:

Original Figure 2:



Revised Figure 2:



5.1.2. Tablet Formulations of ATV, RTV, TDF/FTC FDC, paragraph 2

The following text has been revised:

Tenofovir disoproxil fumarate/ emtricitabine fixed dose combination (TDF/~~3TC~~**FTC** FDC [Truvada])

6.1. Time and Events Schedule, Table 3 Time and Events Table

The following text has been revised:

Child-Pugh Classification: Deletion of the row representing the 'Child-Pugh Classification'.

Bone marker analytes: Deletion of 'X' representing the assessment for bone marker analytes during the Continuation Phase.

The following text (footnote) has been deleted:

~~x: Child-Pugh Score should be calculated using results from the Screening Visit.~~

6.6.1. Virology Endpoints

- Incidence of treatment-emergent genotypic and phenotypic resistance in subjects ~~experiencing virologic failure~~ **who meet confirmed virologic withdrawal criteria**.

10. References

The title of the following reference was formatted incorrectly and is corrected below:

Hill, A, Sabin, C. Designing and interpreting noninferiority trials in naïve and experienced patients. AIDS. 2008;22(8):913-921.

The following text (reference) has been added:

International AIDS Society (IAS)–USA. Update of the Drug Resistant Mutations in HIV-1: March 2013. Topics in HIV Medicine 2013; 21(1): 6-14.

11.2 Appendix 2: Child-Pugh Classification

The following text has been deleted:

~~11.2 Appendix 2: Child-Pugh Classification~~

~~A subject is classified with mild hepatic impairment (Class A) if their overall sum of scores is 5-6 points, moderate hepatic impairment (Class B) if their overall sum of scores is 7-9 points, and severe hepatic impairment (Class C) if their overall sum of scores is 10-15 based on the Child-Pugh system [Pugh, 1973] scoring described in the following table (Table 11). For subjects requiring anticoagulation therapy, discussion with the study medical monitor will be required.~~

~~Table 11 Child-Pugh System~~

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

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

~~Lucey MR, Brown KA, Everson GT, Fung JJ, Gish R, Keeffe EB, et al. Minimal Criteria for Placement of Adults on the Liver Transplant Waiting List Liver Transplantation ans Surgery, Vol. 3, No 6 (November), 1997:pp 628-637~~

~~Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973; 60: 649-649.~~

Section, Appendix and Table numbers affected by deletion of the Child-Pugh Classification have been updated accordingly.

11.7.2. Protocol changes for Amendment 02 (11-AUG-2014) from Amendment 01 (12-AUG-2013)

This protocol amendment applies to sites in the UK only. The amendment was initially implemented as a 'alternative' format amendment, and was brought into the main protocol text at the time of Protocol Amendment 03.

Rationale for Protocol Amendment 02:

The UK Medicines and Healthcare products Regulatory Agency (MHRA) requested the following changes to the UK country specific information on study duration (Appendix 5): i) a specific end date for treatment for subjects in the UK, and ii) removal of the term 'commercially available' in reference to treatment ending when investigational product is 'commercially available'.

The medical monitor information in the Sponsor Information Page has also been updated.

LIST OF SPECIFIC CHANGES:

- **Sponsor Information Page; Medical Monitor Contact Information and Serious Adverse Events (SAE) Contact Information:**

Original Verbatim Text

PPD , MD
Infectious Diseases TAU,
GlaxoSmithKline
5 Moore Drive, N2.2213
Research Triangle Park, NC 27709, USA
Telephone: PPD
Mobile: PPD
Facsimile: PPD
e-mail: PPD

Amended Text

PPD , MD
Infectious Diseases TAU,
GlaxoSmithKline
5 Moore Drive,
Research Triangle Park, NC 27709, USA
Telephone: PPD
Mobile: PPD
Facsimile: PPD
e-mail: PPD

- **Appendix 5: Country Specific Requirements**

Original Verbatim Text

United Kingdom

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

Study Duration

The Continuation Phase is intended to provide access to DTG/ABC/3TC FDC until DTG/ABC/3TC FDC receives local (by country) Regulatory approval and becomes commercially available. Therefore, the duration of the Continuation Phase will vary from country to country and is dependent on the recruitment time for the study and the time taken to achieve local approval for marketing. For subjects in the UK, estimating an 18 month recruitment period, Marketing Application Authorisation (MAA) submission in 2013, and allowing for regulatory review time of the MAA, the Continuation Phase is

anticipated to conclude in the UK in approximately 1Q2015, and subjects who complete the randomized phase of the study after this date are expected transition directly to commercial supplies.

Amended Text

United Kingdom

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

Study Duration

In this study, the date of last study treatment administration in the UK will be determined by the completion of the 48 week randomized phase of the study for the last UK subject enrolled (it will not be determined by the completion of the Continuation Phase). The last subject will be enrolled by February 2015, and hence the last study treatment administration will occur by 28 February 2016.

(Note: The Continuation Phase is intended to provide subjects on DTG/ABC/3TC FDC with post-study access to DTG/ABC/3TC FDC until it becomes available in their countries. For subjects in the UK, the Continuation Phase is anticipated to conclude by 31 March 2015, when DTG/ABC/3TC FDC is anticipated to become available).

11.7.3. Protocol changes for Amendment 03 (19-JUN-2018) from Amendment 02 (11-AUG-2014)

This protocol amendment applies to all participating sites.

Rationale for Protocol Amendment 03:

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.

- 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, and refer to the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential.

- The withdrawal criteria (Section 4.5.) were updated to include a reminder that females of reproductive potential who change their minds and desire to be pregnant, or who state they no longer are willing to comply with the approved pregnancy avoidance methods, should also be withdrawn from the study.

- The Time and Events table (Section 6.1.) was updated to include a reminder for investigators to check at every visit that females of reproductive potential are avoiding pregnancy.

- Appendix 6 was added: Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential

Administrative updates were made

LIST OF SPECIFIC CHANGES

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

- **Authors**

PPD

- **Sponsor Information Page; Medical Monitor Contact Information and Serious Adverse Events (SAE) Contact Information:**

PPD ~~, MD~~
~~Infectious Diseases TAU,~~
~~GlaxoSmithKline~~
~~5 Moore Drive, N2.2213~~
~~Research Triangle Park, NC 27709, USA~~
~~Telephone:~~ PPD
~~Mobile:~~ PPD
~~Facsimile:~~ PPD
~~e-mail:~~ PPD

PPD, MD
ViiV Healthcare,
5 Moore Drive,
Research Triangle Park, NC 27709, USA
Mobile: PPD
Facsimile: PPD
e-mail: PPD

- **Abbreviations**

FRP **Females of Reproductive Potential**

- **Section 1.3.1. Risk Assessment**

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy[1]
Investigational Product (IP) [DTG/ABC/3TC] Refer to IB for additional information on DTG and DTG/ABC/3TC Refer to approved country product label for additional information on ABC/3TC		
DTG: Neural tube defects	**In one ongoing birth outcome surveillance study in Botswana, early results from an unplanned interim analysis show that 4/426 (0.9%) of women who were taking DTG when they became pregnant had babies with neural tube defects compared to a background rate of 0.1%.**	**1. A female subject is eligible to participate if she is not pregnant, not lactating, and, if she is a female of reproductive potential, agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see Appendix 6, Section 11.6), until at least 2 weeks after discontinuation of IP** **2. Women who are breastfeeding or plan to become pregnant or breastfeed during the study are excluded;** **3. Women who become pregnant, or who desire to be pregnant while in the study, or who state they no longer are willing to comply with the approved pregnancy avoidance methods, will have study treatment discontinued and withdrawn from the study.** **4. Females of reproductive potential are reminded re: pregnancy avoidance and adherence to contraception requirements at every study visit.** **5. Pregnancy status is monitored at every study visit**

- **Section 4.2. Inclusion Criteria**

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

   a. is of non-child-bearing potential either defined as 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:

- **Refer to Appendix 6, Section 11.6: Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential**.
- ~~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);~~
- ~~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 sterilization *prior to the female subject's entry* into the study and this male is the sole partner for that subject;~~
- ~~Any other method with published data showing that the expected failure rate is <1% per year.~~
- ~~Approved hormonal contraception for subjects randomized to the DTG/ABC/3TC arm (see the SPM for a listing of examples of approved hormonal contraception).~~
- ~~Approved hormonal contraception and a barrier method for subjects randomized to the ATV+RTV+TDF/FTC arm.~~

Any contraception method must be used consistently, in accordance with the approved product label and for at least 2 weeks after discontinuation of IP. **The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.**

- **Section 4.5. Withdrawal Criteria**

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

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

- **Section 6.1. Time and Events Schedule**

h. Pregnancy testing. Women of childbearing potential only. S=serum, U=urine. **Remind females of reproductive potential of the need to avoid pregnancy while in study and adherence to the study's contraception requirements.**

- **Section 10. References**

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.

GlaxoSmithKline Document Number RM2007/00683/~~06~~**11**: GSK1349572 Clinical Investigator's Brochure.~~ February 2013.~~ **Version 11, October 2017.**

References to the DTG IB were also updated throughout the protocol to reference the current DTG IB.

- **Section 11.6, Appendix 6**

A new Section 11.6, Appendix 6 was inserted; the previous Appendix 6 (Section 11.6, Appendix 6 Protocol Changes) was updated to Section 11.7, Appendix 7.

Appendix 6: Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

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

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

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

Reference

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