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

## Overall Design

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

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

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

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

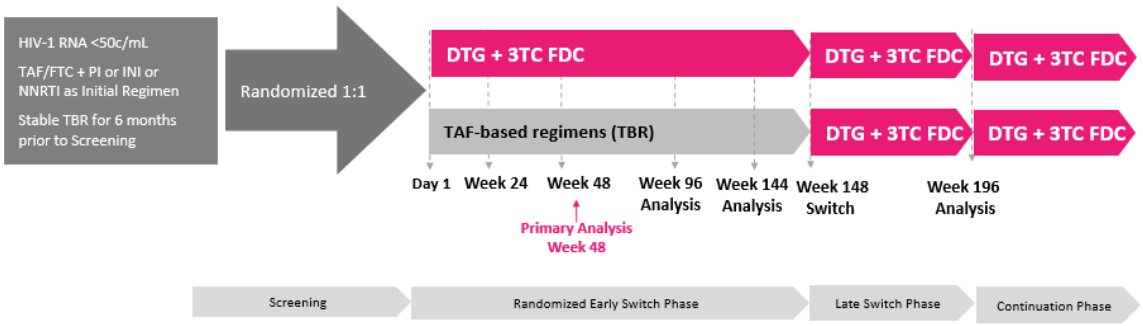
| Objective | Endpoint |
|---|---|
| **Exploratory** | |
| To evaluate the effect of patient characteristics (e.g., demographic factors, Baseline CD4) on antiviral and immunological responses to DTG + 3TC compared to TBR | • Proportion of subjects by subgroup(s) (e.g., by age, gender, Baseline CD4) with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

An Independent Data Monitoring Committee (IDMC) will be instituted to ensure external objective medical and/or statistical review of efficacy and safety in order to protect the ethical interests and well-being of subjects and to protect the scientific validity of the study. An ad-hoc review of data by the IDMC will be triggered whenever the number of confirmed virologic withdrawals (CVWs) exceeds thresholds pre-specified in the IDMC charter. Full details of the methods, timing, decision criteria and operating characteristics will be pre-specified in the IDMC Charter. Communication received from the IDMC regarding the status of the study will be shared with investigators in a timely manner.

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

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

**Figure 1 Study Schematic**




## 4.2. Treatment Arms and Duration

### 4.2.1. Screening Period (Up to 28 days)

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

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

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

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

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

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

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

## 7.1. Time and Events Table

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

| Procedures | Screening Visit[a] | Open-label Randomised Early Switch Phase | | | | | | | | | | | | | | Switch Visit | Withdrawal | Follow-up[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Baseline / Day 1 | Week | | | | | | | | | | | | | | | |
| | | | 4 | 8 | 12 | 24 | 36 | 48 | 60 | 72 | 84 | 96 | 108 (optional)[b] | 120 | 132 (optional)[b] | 144 | 148[c] | |
| **Clinical and Other Assessments** | | | | | | | | | | | | | | | | | | |
| Written informed consent | X | | | | | | | | | | | | | | | | | |
| Inclusion/Exclusion criteria[e] | X | X | | | | | | | | | | | | | | | | |
| Demography | X | | | | | | | | | | | | | | | | | |
| Prior ART history | X | | | | | | | | | | | | | | | | | |
| Medical history[f] | X | | | | | | | | | | | | | | | | | |
| Current medical conditions | X | | | | | | | | | | | | | | | | | |
| Cardiovascular risk assessment, including vital signs[g] | X | | | | | | | | | | | | | | | | | |
| Body Weight (BMI will be calculated within the eCRF) | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| HIV risk factors and mode of transmission | | X | | | | | | | | | | | | | | | | |
| CDC HIV-1 classification | X | X | | | | | | | | | | | | | | | | |
| HIV associated conditions | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Columbia Suicidality Severity Rating Scale | | X[h] | X | X | X | X | X | X | X | X | X | X | X | X | X | | X | |

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

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

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

a. As soon as all Screening results are available, randomization may occur.
b. This optional study visit is ONLY to be conducted in countries that require visits every 3 months per standard of care.
c. Subjects with plasma HIV-1 RNA ≥50 c/mL at Week 144 must have HIV-1 RNA level re-assessed by a second measurement performed 2-4 weeks later. Subjects should have received full doses of study treatment for at least 2 weeks at the time of HIV-1 RNA re-assessment. Subjects randomized to DTG + 3TC do not attend a Week 148 switch visit.
d. An in-clinic Follow-Up visit will be conducted 4 weeks after the last dose of study medication for subjects with the following conditions at the last on-study visit: ongoing AEs, serious adverse events (SAEs) regardless of attributability, any laboratory abnormalities considered to be AEs or potentially harmful to the subject. Only the laboratory tests necessary to evaluate the AE/SAE/laboratory abnormality should be collected.
e. Inclusion/exclusion criteria will be assessed fully at the Screening visit. Changes between the Screening visit and the Day 1 visit should be considered to ensure eligibility, including review of additional assessments performed at Day 1. Genotypic resistance testing results MUST be provided to ViiV after screening and before randomization.
f. Full medical history will be conducted prior to randomization and include assessments of cardiovascular, metabolic (e.g., Type I or II diabetes mellitus), psychiatric (e.g., depression), renal (e.g., nephrolithiasis, nephropathy, renal failure), and bone disorders.
g. Assessment for cardiovascular risk will include height, weight, blood pressure, smoking status and history, pertinent medical conditions (e.g., hypertension, diabetes mellitus), and family history of premature cardiovascular disease. BMI will be calculated within the eCRF.
h. On Day 1, the electronic Columbia Suicidality Severity Rating Scale eC-SSRS, patient completed questionnaire) is to be administered prior to randomization.

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

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

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

Subjects who meet all entry criteria are randomized and assigned a randomization number. Subjects not meeting all inclusion and exclusion criteria at initial screen may be rescreened and receive a new subject number one time unless they were excluded for reason of having exclusionary historic genotypic resistance or for a viral load ≥ 50c/mL at time of screening. Subjects who are randomized into the trial and subsequently withdrawn from the study for any reason may not be rescreened.

### 7.2.2. Baseline Assessments

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

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

## 7.3. Efficacy

### 7.3.1. Efficacy Evaluations

**Plasma HIV-1 RNA**

Plasma for quantitative HIV-1 RNA will be collected according to the Time and Events Table (Section 7.1). Methods to be used may include but are not limited to the Abbott Realtime HIV-1 Assay lower limit of quantitation 40 c/mL. In some cases (e.g., where the plasma HIV-1 RNA is below the lower limit of detection for a given assay) additional exploratory methods may be used to further characterize plasma HIV-1 RNA levels.

**Lymphocyte Subsets**

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

**CDC HIV-1 Classification and HIV Associated Conditions**

HIV-associated conditions will be recorded as per the Time and Events Table (Section 7.1). HIV associated conditions will be assessed according to the 2014 CDC Revised Classification System for HIV Infection in Adults (see Section 13.7). When assessing CDC stage at screening consider only the latest available CD4 T-cell count, including CD4 T-cell count at screening. If a stage-3–defining opportunistic illness has been diagnosed up to screening, then the stage is 3 regardless of CD4 T-cell count test results.

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

Indicators of clinical disease progression are defined as:

CDC Stage 1 at enrolment → Stage 3 event;

CDC Stage 2 at enrolment → Stage 3 event;

CDC Stage 3 at enrolment → New Stage 3 Event;

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

#### 7.3.1.1. Primary Efficacy Endpoint

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

#### 7.3.1.2. Secondary Efficacy Endpoints

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

#### 7.3.1.3. Exploratory Efficacy Endpoints

- Proportion of subjects with plasma HIV-1 RNA <50 c/mL by patient subgroup(s) (e.g., by age, gender, Baseline CD4+) at Week 24, 48, 96 and 144 using the Snapshot algorithm for the ITT-E population

#### 7.4.1.2. Method of Detecting AEs and SAEs

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

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

#### 7.4.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.

#### 7.4.1.4. Cardiovascular and Death Events

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

The CV CRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific CV section of the CRF within one week of receipt of a CV Event data query prompting its completion.

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

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

The events or outcomes listed in the CDC Classification System for HIV-1 Infections (Section 13.7) will be recorded on the HIV-Associated Conditions eCRF page if they occur. However, these individual events or outcomes, as well as any sign, symptom, diagnosis, illness, and/or clinical laboratory abnormality that can be linked to any of these events or outcomes are not reported to ViiV/GSK as AEs and SAEs even though such event or outcome may meet the definition of an AE or SAE, **unless the following conditions apply**:

- The investigator determines that the event or outcome qualifies as an SAE under part 'f' of the SAE definition (see Section 13.8.2), or
- The event or outcome is in the investigator's opinion of greater intensity, frequency or duration than expected for the individual subject, or

additional parameters to be tested are listed in Table 1. Labs will be graded automatically by the central lab according to the DAIDS toxicity scales (See Section 13.9 “Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events”).

genotype/phenotype data.

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

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

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study or within 5 days after the last dose of study treatment should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

### 7.4.7. Suicidal Risk Monitoring

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

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

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

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

## 7.8. Pharmacokinetic Assessments

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

# 8. DATA MANAGEMENT

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

# 9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

## 9.1. Hypotheses

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

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

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

## 9.2. Sample Size Considerations

### 9.2.1. Sample Size Assumptions

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

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

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

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

#### 9.2.1.1. Rationale for non-inferiority margin

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

# 10. STUDY GOVERNANCE CONSIDERATIONS

## 10.1. Posting of Information on Publicly Available Clinical Trial Registers

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

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

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

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

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

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Obtaining signed informed consent
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- ViiV/GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

**Table 4 Sparse Pharmacokinetic Sampling Schedule**

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

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

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

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

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

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

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

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

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

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

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

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

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

### 11.1.4. Bioanalysis of DTG and 3TC Samples

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

### 11.1.5. Pharmacokinetic Populations

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

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

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

### 11.1.6. Pharmacokinetic Analyses

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

| | |
|---|---|
| E/C/F/TAF | Elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide |
| E/C/F/TDF | Elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| eC-SSRS | Electronic Columbia Suicidality Severity Rating Scale |
| eDM | Electronic Data Management |
| EFV | Efavirenz |
| eGFR | Estimated glomerular filtration rate |
| EMA | European Medicines Agency |
| EQ-5D-5L | European Quality of Life-5 Dimensions-5 Levels |
| ETR | Etravirine |
| EU | European Union |
| EVG | Elvitegravir |
| FDA | Food and Drug Administration |
| FDC | Fixed-dose combination |
| FSFV | First subject first visit |
| FTC | Emtricitabine |
| GCP | Good Clinical Practice |
| GCSP | GSK's Global Clinical Safety and Pharmacovigilance |
| GSK | GlaxoSmithKline |
| GFR | Glomerular Filtration rate |
| HAART | Highly active ART therapy |
| HbA1c | Glycated henoglobin |
| HBsAb | Hepatitis B surface Antibody |
| HBsAg | Hepatitis B surface Antigen |
| HBV | Hepatitis B virus |
| HCV | Hepatitis C virus |
| HDL | High density lipoprotein |
| HDPE | High density polyethylene |
| HIV | Human immunodeficiency virus |
| HIV TSQ | HIV treatment satisfaction questionnaire |
| HLA | Human leukocyte antigen |
| HOMA-IR | Homeostasis model of assessment-insulin resistance |
| Hs-CRP | High-sensitivity C reactive protein |
| HSR | Hypersensitivity reaction |
| IB | Investigator's Brochure |
| ICH | International Conference on Harmonisation |
| IDMC | Independent data monitoring committee |
| IEC | Independent Ethics Committee |
| IgM | Immunoglobulin M |
| IL-6 | Interleukin-6 |
| INI | Integrase inhibitor |
| INSTI | Integrase strand transfer inhibitor |
| INR | International normalized ratio |
| IP | Investigational Product |
| IRB | Institutional Review Board |

#### 13.2.1.3. Decline in Renal Function

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

Subjects who experience progression to an estimated GFR (using the CKD-EPI-creatinine) of < 30 mL/min/1.73m$^2$ must return for a confirmatory assessment within 2 weeks [Levey, 2009]. A urinalysis, urine albumin/creatinine and urine protein/creatinine ratios, serum cystatin C and an estimated GFR using the CKD-EPI (cystatin C) [Inker, 2012] should be done at this confirmatory visit. If an estimated GFR of < 30 mL/min/1.73m$^2$ is confirmed using the CKD-EPI (cystatin C), then study treatment should be discontinued and the subject withdrawn from the study (as dose adjustment is needed for NRTIs, which is not possible in a study of a fixed-dose combination tablet).

#### 13.2.1.4. Proteinuria

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

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

#### 13.2.1.5. Allergic reaction

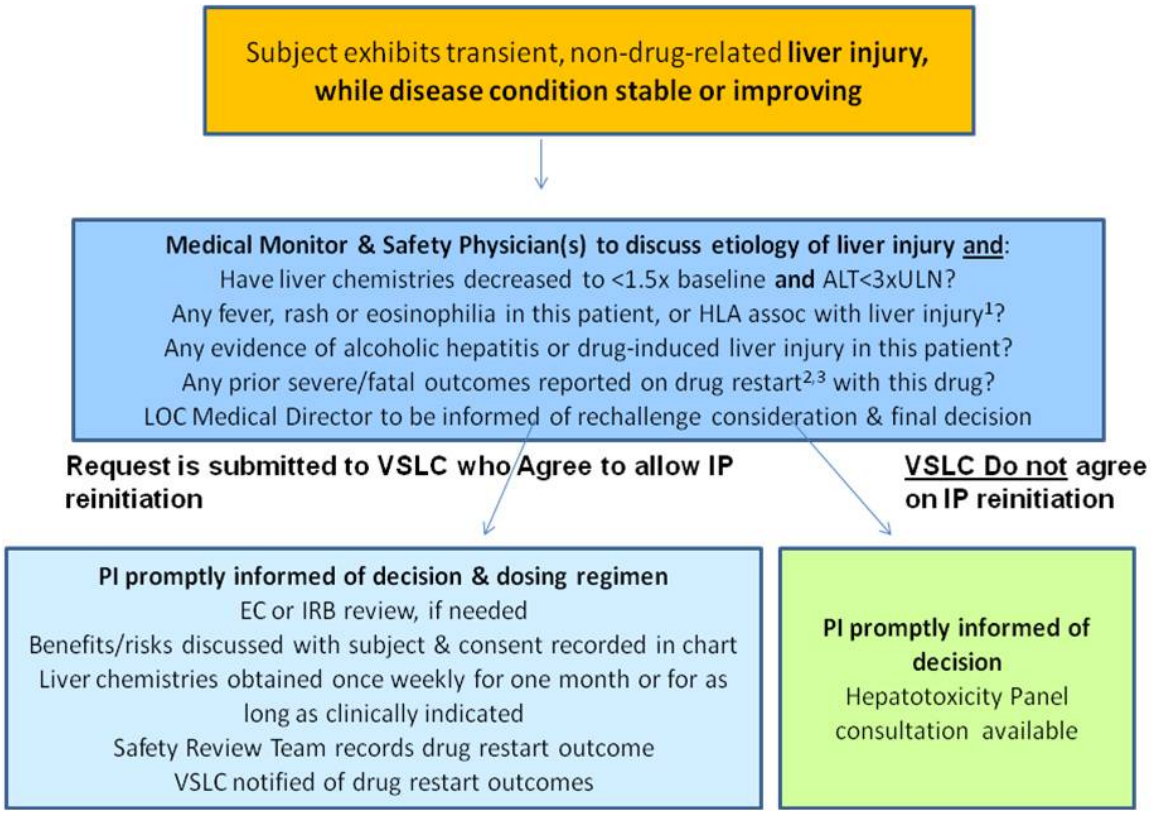
Subjects may continue study drug for Grade 1 or 2 allergic reactions at the discretion of the Investigator. The subject should be advised to contact the Investigator immediately if there is any worsening of symptoms or if further systemic signs or symptoms develop. Antihistamines, corticosteroids, or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

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

| | |
|---|---|
| **MONITORING:**<br>• Make every reasonable attempt to have subjects return to clinic within **24 hours** for repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments.<br>• Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline<br>• A specialist or hepatology consultation is recommended | within 60 hours after last dose[4]<br>• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).<br>• Fractionate bilirubin, if total bilirubin ≥2xULN<br>• Obtain complete blood count with differential to assess eosinophilia<br>• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins).<br>• Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.<br>• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash as relevant on the AE report form<br>• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.<br>• Record alcohol use on the liver event alcohol intake case report form |

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. PK sample may not be required for subjects known to be receiving placebo or non- ViiV/GSK standard-of-care treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be

**Figure 4 VSLC process for drug restart approval or disapproval**




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

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

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

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

condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

### 13.8.2. Definition of Serious Adverse Events

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

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

**a) Results in death**

**b) Is life-threatening**

NOTE:

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

**c) Requires hospitalization or prolongation of existing hospitalization**

NOTE:

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

**d) Results in disability/incapacity**

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza,

and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption

**e) Is a congenital anomaly/birth defect**

**f) Other situations:**

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

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

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

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

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

### 13.8.3. Definition of Cardiovascular Events

**Cardiovascular Events (CV) Definition:**

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

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

### 13.8.4. Sentinel Events

**Sentinel Event Definition:**

A sentinel event is a ViiV/GSK -defined SAE that is not necessarily drug-related but has been associated historically with adverse reactions for other drugs and is therefore worthy of heightened pharmacovigilance. Medical monitor review of all SAEs for possible sentinel events is mandated at ViiV/GSK. The medical monitor may request additional clinical information on an urgent basis if a possible sentinel event is identified on SAE review. The current ViiV/GSK-defined sentinel events are listed below:

- Acquired Long QT Syndrome
- Agranulocytosis/Severe neutropenia
- Anaphylaxis and anaphylactoid reactions
- Hepatotoxicity
- Acute renal failure
- Seizure
- Stevens Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN)

### 13.8.5. Recording of AEs and SAEs

**AEs and SAE Recording:**

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

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

### 13.8.6. Evaluating AEs and SAEs

**Assessment of Intensity**

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the categories in the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE Grading Table") in Section 13.9:

- Grade1 / Mild
- Grade 2 / Moderate
- Grade 3 / Severe
- Grade 4 / Potentially life threatening
- Grade 5 / Death

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

**Assessment of Causality**

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to ViiV/GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to ViiV/GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

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

### VERSION 2.1, March 2017

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

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

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

***Major Clinical Conditions Cardiovascular***

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

| PARAMETER | GRADE 1 MILD | GRADE 2 MODERATE | GRADE 3 SEVERE | GRADE 4 POTENTIALLY LIFE-THREATENING |
|---|---|---|---|---|
| **Blood Pressure Abnormalities**[1]<br>***Hypertension*** *(with the lowest reading taken after repeat testing during a visit)*<br>*≥ 18 years of age* | 140 to < 160 mmHg systolic<br>OR<br>90 to < 100 mmHg diastolic | ≥ 160 to < 180 mmHg systolic<br>OR<br>≥ 100 to < 110 mmHg diastolic | ≥ 180 mmHg systolic<br>OR ≥ 110 mmHg diastolic | Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated |
| *< 18 years of age* | > 120/80 mmHg | ≥ 95$^{th}$ to < 99$^{th}$ percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic) | ≥99$^{th}$ percentile +5mmHg adjusted for age, height, and gender (systolic and/or diastolic) | Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated |
| ***Hypotension*** | No symptoms | Symptoms corrected with oral fluid replacement | Symptoms AND IV fluids indicated | Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure |
| **Cardiac Ischemia or Infarction**<br>*Report only one* | NA NA | NA | New symptoms with ischemia (stable angina) OR New testing consistent with ischemia | Unstable angina OR Acute myocardial infarction |
| **Heart Failure** | No symptoms AND Laboratory or cardiac imaging abnormalities | Symptoms with mild to moderate activity or exertion | Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR Intervention indicated (e.g., oxygen) | Life-threatening consequences OR Urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant) |

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

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

## Treatment Arms and Duration

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

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

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

- DTG + 3TC FDC is locally approved for use as a 2-drug regimen, and available to subjects (e.g., through public health services or through their usual health insurance payer), or
- the subject no longer derives clinical benefit, or
- the subject meets a protocol-defined reason for discontinuation, or
- development of the DTG plus 3TC dual regimen is terminated.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

## 4.5. Dose Justification

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

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

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

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

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

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

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

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

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

i. Limited physical examination to include blood pressure at Day 1 (recorded in eCRF) for Framingham score assessment. Blood pressure to be measured after resting in a semi-supine position for at least 5 minutes.
j. A 12-lead ECG will be performed after resting in a semi-supine position for at least 5 minutes.
k. Only SAEs related to study participation or to a concomitantly administered ViiV/GSK product will be collected between obtaining informed consent and administration of study drug at Day 1.
l. Willingness to Switch Survey must be done prior to randomization.
m. Questionnaire/Surveys are recommended to be administered at the beginning of the visit before any other assessments are conducted. Only conduct questionnaires/surveys at Withdrawal if occurring prior to Week 196.
n. See Virologic Withdrawal and Stopping Criteria Section of protocol (Section 5.4).
o. Plasma samples for storage will be collected at each visit starting at Screening, including unscheduled visits (e.g. for HIV-1 RNA levels and immunological parameters). These samples will be used when needed such as when samples are lost, arrive at the laboratory unevaluable, or for genotypic and/or phenotypic analyses when subjects meet Suspected and Confirmed Virologic Withdrawal criteria.
p. An overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable.
q. Collect sample for these assessments ONLY if the Withdrawal visit occurs at Week 24, 48, 96, 144 or 196.
r. A morning specimen is preferred. To assess renal biomarkers: urine albumin/creatinine ratio; urine protein/creatinine ratio; and urine phosphate.
s. Women of childbearing potential only. S=serum, U=urine. Pregnancy events will be captured starting at Day 1 following exposure to study drug.
t. Remind females of reproductive potential of the need to avoid pregnancy while in study and adherence to the study's contraception requirements.
u. Beginning after Week 96, if study visits are every 24 weeks, participants who are women of child bearing potential must also do a home-based urine pregnancy test approximately every 12 weeks between study visits at approximately Weeks 108, 132, 160 and 184 and during the Continuation Phase. Site staff must contact the participants who are women of child bearing potential to remind them to complete the test and to verify and record pregnancy test results in the source documents. The site must also complete the pregnancy status eCRF if a pregnancy occurs and report the pregnancy to ViiV/GSK per Section 13.3.2.
v. Local serum pregnancy test on Day 1 is allowed if it can be done, and results obtained, within 24 hours prior to randomization
w. HBV DNA testing will be performed for subjects with positive anti-HBc and negative HBsAg and negative anti-HBs (past and/or current evidence). Subjects will have to return to the clinic to provide a sample for HBV DNA testing prior to randomisation.
x. Blood sample for insulin, HbA1c, and renal and bone biomarker assessments: **Renal:** Cystatin C; Beta-2-Microglobulin; Retinol Binding Protein (RBP); **Bone:** bone specific alkaline phosphatase, procollagen type 1-N-propeptide, type 1 collagen cross-linked C-telopeptide, osteocalcin, 25 hydroxy-Vitamin D.
y. Whole blood (Virology) may be used for virologic analyses as described in the protocol.
z. Whole blood will be used for telomere length evaluation at Day 1, Week 48, Week 96, Week 144, Week 196 and at the Withdrawal visit.
aa. Collect sample for these assessments ONLY if the Withdrawal visit occurs at Week 48, 96, 144 or 196
bb. PBMCs will be collected, cryopreserved and stored in a subset of sites. These samples will be used for the measurement of telomerase activity.
cc. Blood sample for inflammation biomarker assessments: IL-6, hs-CRP, d dimer, sCD14, sCD163.
dd. At Screening, a subject number will be generated.
ee. PK sampling in subjects from the DTG/3TC FDC arm only, as detailed in Section 11.
ff. Intensive PK sampling in a subset of subjects from the DTG/3TC FDC arm at select sites at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 10 and 24 hours post-dose. On the intensive PK day, patients are required to fast from 8 hours prior to dosing and then through 4 hours post-dose. Detailed in Section 11.
gg. At Week 4, subjects who performed intensive PK do not perform Sparse PK sampling.
hh. Subjects must return to the clinic for a Week 200 End of Study visit when transitioning to commercial supplies or to an alternate ART regimen, if appropriate. Do not dispense

- Change from Baseline in CD4+ cell counts at Weeks 24, 48, 96, 144 and 196 by patient subgroups

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

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

## 7.4. Safety

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

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

The definitions of an AE or SAE can be found in Section 13.8.

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

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

- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a ViiV/GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- AEs will be collected from the start of Study Treatment until the follow-up contact at the timepoints specified in the Time and Events Table.
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- All SAEs will be recorded and reported to ViiV/GSK within 24 hours, as indicated in Section 13.8.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify ViiV/GSK.

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

- Death occurring for any reason during a study, including death due to a disease-related event, will always be reported promptly.

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

#### 7.4.1.6. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to ViiV/GSK (or designee) of SAEs related to study treatment (even for non- interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

ViiV has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. ViiV will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

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

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

### 7.4.2. Pregnancy

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

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

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

**Table 1 Protocol Required Safety Laboratory Assessments**

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

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

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

be completed and reported to ViiV/GSK within 1 week of the investigator diagnosing a possible suicidality-related AE.

## 7.5. Biomarkers

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

Renal biomarkers:

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

Bone biomarkers:

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

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

Inflammation biomarkers:

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

Insulin, HbA1c, and HOMA-IR

Telomere function:

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

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

## 7.6. HIV-1 Polymerase Viral Genotyping and Phenotyping

Whole venous blood samples will be obtained from each subject to provide plasma for storage samples according to the Time and Events Table (for potential viral genotypic

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

#### 9.2.1.2. Response and Virologic Failure rate assumptions

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

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

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

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

## 10.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and ViiV/GSK procedures, GSK monitors, or any third parties conducting the study on behalf of ViiV/GSK, will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and ViiV/GSK requirements.
- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

ViiV/GSK will monitor the study and site activity to verify that the:

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

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

## 10.4. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

## 10.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and ViiV/GSK Standard Operating Procedures.
- ViiV/GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If ViiV/GSK determines such action is needed, ViiV/GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, ViiV/GSK will provide advance

### 11.1.7. Population PK

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

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

#### 13.2.1.6. Rash

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

Subjects with an isolated Grade 1 rash may continue study drug at the Investigator's discretion. The subject should be advised to contact the Investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms appear, or if mucosal involvement develops.

Subjects may continue study drug for an isolated Grade 2 rash. However, study drug (and all other concurrent medication(s) suspected in the Investigators causality assessment) should be permanently discontinued for any Grade ≥2 rash that is associated with an increase in ALT. The subject should be advised to contact the physician immediately if rash fails to resolve (after more than two weeks), if there is any worsening of the rash, if any systemic signs or allergic symptoms develop, or if mucosal involvement develops.

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

The rash and any associated symptoms should be reported as adverse events and appropriate toxicity ratings should be used to grade the events (based on DAIDS toxicity gradings, Section 13.9.

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

#### 13.2.1.7. Hypertriglyceridemia/Hypercholesterolemia

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

collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

## References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-84.

**Table 7 Liver Chemistry Increased Monitoring Criteria With Continued Therapy**

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

## Principal Investigator Actions:

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

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

### Restart safety outcomes:

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

## References

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

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

Papay JI, Clines D, Rafi R, et al. Drug-induced liver injury following positive drug rechallenge. Regul Tox Pharm. 2009; 54:84-90.

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

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

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

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

## *Cardiovascular*

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

[2] As per Bazett's formula